HOUSE OF COMMONS SESSION 1996–97

SCIENCE AND TECHNOLOGY COMMITTEE

Fifth Report

THE CLONING OF ANIMALS FROM ADULT CELLS

Volume II

Minutes of Evidence and Appendices

Ordered by The House of Commons *to be printed*
18 March 1997

LONDON : THE STATIONERY OFFICE
£9.70

HC 373-II

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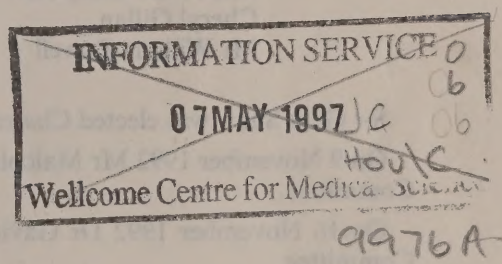

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The Science and Technology Committee is appointed under Standing Order No 130 to examine the expenditure, administration and policy of the Office of Science and Technology and associated public bodies.

The Committee consists of 11 Members. It has a quorum of three.

The Committee has power:

(a) to send for persons, papers and records, to sit notwithstanding any adjournment of the House, to adjourn from place to place, and to report from time to time;

(b) to appoint specialist advisers either to supply information which is not readily available or to elucidate matters of complexity within the Committee's order of reference;

(c) to communicate to any other such committee and to the Committee of Public Accounts and to the Deregulation Committee its evidence and any other documents relating to matters of common interest; and

(d) to meet concurrently with any other such committee for the purposes of deliberating, taking evidence, or considering draft reports.

Unless the House otherwise orders, all Members nominated to the Committee continue to be members of it for the remainder of the Parliament.

The following were nominated Members of the Committee on 13 July 1992:

Mr Spencer Batiste
Dr Jeremy Bray
Mr Malcolm Bruce
Mrs Anne Campbell
Cheryl Gillan
Mr William Powell
Sir Giles Shaw
Sir Trevor Skeet
Dr Gavin Strang
Sir Gerard Vaughan
Dr Alan W Williams

Sir Giles Shaw was elected Chairman on 15 July 1992.

On 9 November 1992 Mr Malcolm Bruce was discharged and Mr Andrew Miller added to the Committee.

On 16 November 1992 Dr Gavin Strang was discharged and Dr Lynne Jones added to the Committee.

On 7th November 1995 Cheryl Gillan and Mr William Powell were discharged and Mr Ian Bruce and Mr Patrick Thompson were added to the Committee.

The cost of printing and publishing this Volume is estimated by The Stationery Office at £2,700.

LIST OF WITNESSES

MEMORANDUM INCLUDED IN THE MINUTES OF EVIDENCE

LIST OF APPENDICES TO THE MINUTES OF EVIDENCE

UNPRINTED MEMORANDA

Additional memoranda have been received from the following and have been reported to the House, but to save printing costs they have not been printed and copies have been placed in the House of Commons Library where they may be inspected by Members. Other copies are in the Record Office, House of Lords, and are available to the public for inspection. Requests for inspection should be addressed to the Record Office, House of Lords, London S.W.1. (Tel 0171-219-3074). Hours of inspection are from 9.30 am to 5.30 pm on Mondays to Fridays.

Memorandum from the Church of Scotland (CLE 11)

Letter and attachments from the Genetics Interest Group (CLE i)

MINUTES OF EVIDENCE

TAKEN BEFORE THE SCIENCE AND TECHNOLOGY COMMITTEE

WEDNESDAY 5 MARCH 1997

Members present:

Sir Giles Shaw, in the Chair

Mr Spencer Batiste
Dr Jeremy Bray
Mr Ian Bruce
Mrs Anne Campbell
Mr Andrew Miller
Sir Trevor Skeet
Sir Gerard Vaughan

Examination of Witnesses

MRS RUTH DEECH, Chairwoman, MRS SUZANNE MCCARTHY, Chief Executive, MR GRAHAM MILES, Legal Adviser, MR DAVID THORNE, Licensing Manager, MS BEATRICE HEALES, Policy Adviser, Human Fertilisation and Embryology Authority, examined.

Chairman

1. Mrs Deech, can I thank you and your colleagues for coming this morning at short notice and I know at a rather busy time for you in relation to this particular issue, but we felt it right to conduct a fairly modest little inquiry at least into certain consequences that seemed to us to flow from the information that we have about the cloning exercise at Roslin. One such was clearly a matter of dealing with the law in its current form in relation to the cloning experiment itself and related matters. So this session was the first we felt we ought to be involved in. Consequently, we are seeing, as it so happens, the MRC later today on the issue in relation to the human point of view, on the medical point of view, on the application and so on, and tomorrow we shall be meeting the Professor in charge and members of the team from Roslin itself. So thank you for responding and thank you for bringing your colleagues. I know that we will hear from you your views about the law in its state as it applies and whether or not you think it is sufficient to deal with public anxiety which appears to be aroused. Do you wish to make a short statement at the outset or would you like to go straight into questions?

(*Mrs Deech*) Perhaps I could just set the scene for you, Chairman. I am surrounded by colleagues. On my left, our lawyer who will share with me any legal points that we shall be raising, which indeed we will, Graham Miles. On his left is a member of the HFEA's policy team. On my right is the Chief Executive, Suzanne McCarthy, and on her right, the gentleman in charge of licensing, Mr David Thorne, who will help out with the details of licensing which may be important. As you know, we have had fairly short notice to deal with this, but cloning and related issues have been on our mind for a number of years and we are well aware of the public anxiety and the problems that this causes. Therefore, we welcome the opportunity to discuss this issue with you. We had already started to identify possible concerns about the use of this technique to produce human embryos and on a crucial point in the Act, which is the definition of an embryo, we are about to instruct counsel on the definition. Much depends on the definitions of embryo, gamete and fertilisation in the Act. I am pleased to say, in a rather proud way perhaps, that Britain has led the world in the regulation of in vitro fertilisation treatment and allied treatments. We believe that we are fortunate in already having a statutory framework in place which may just need some slight amendment or tweaking, if I can put it that way, to cope with the current public concerns. We already have a pretty good statutory framework, but science moves on apace and phrases and definitions that were the state of the art in 1990 are perhaps not quite comprehensive enough to deal with the newest scientific developments and, of course, we envisage that in another five years or so there may well be further concerns that none of us could envisage today. But we have a framework which is pretty good and which we can continue to develop. As I said, we need to get a firm opinion on the definition of embryo given in the HFEA Act 1990. If that definition includes embryos produced through cloning then we are confident in saying that this Authority would be able to regulate any forms of cloning that are not already specifically forbidden by the Act through our licensing procedure. If the definition of embryo given in the Act is not sufficiently wide then there may be concerns about the ability of the Authority to regulate some aspects of the new technique. I would emphasise that in our view there is no need to panic or even to hurry. There are a number of fall-back positions and we do not believe that anything that might give rise to public anxiety can possibly happen, for example, in the next few months, which would give Parliament ample time to amend the Act and receive advice on the definition of embryo and fertilisation, if necessary. If the Act is to be amended then our view is that we still ought to keep open a flexible approach, though this is for Parliament to decide. Parliament might take the view that there should be an absolute statutory ban that would involve another section to the Act or it might take the view that possibly in years to come there might be certain beneficial aspects of this new procedure and that you would want to leave the door open, as indeed it is in the statutory framework, for project by project to be assessed and regulated.

2. Thank you for that, Mrs Deech. I need hardly say that you have already touched on some of the areas which this Committee wanted to ask questions

[**Chairman** *Cont*]
about. Equally, it is our duty to inform just not ourselves but Parliament also and therefore we will be asking questions on what you have stated and perhaps a little beyond it. Could I just, for the record, have which parts of the Human Fertilisation and Embryology Act would apply to cloning humans?

(*Mrs Deech*) My answer in the end will be a multi-layered answer because there are a number of levels of control in the Act. I start at the top where there are direct statutory bans. Section 3(3)(d) of the 1990 Act prohibits the cloning of human embryos by the nuclear replacement of embryos, i.e. it prohibits the replacing of the nucleus of an embryo with a nucleus taken from the cell of any person, embryo, etcetera. I should perhaps hasten to add that that is not an exact description of the latest technique carried out at the Roslin Institute. But this particular statutory prohibition covers, for example, the cloning of monkeys, which I believe was carried out in Oregon very recently, and it would cover the sort of technique that was in the news a year ago when twin sheep called Megan and something else, I believe, were produced, but it does not cover the technique most recently announced a few days ago by the Roslin Institute. So that is section 3(3)(d). Then section 3(1)(b) of the Act requires that the use of any embryo can only be carried out with a licence from the Authority. Much turns on the definition of embryo, but I can tell you that as far back as February 1994, in response to an earlier incident, the Authority announced that it would not grant licences neither for treatment nor research for embryo splitting with the purposes of developing cloning for treatment. So we have already got a direct ban on embryo splitting. Schedule 2 paragraphs 1(4) and 3(4) of the Act prohibit genetic manipulation of embryos. Again, that may not perhaps cover what happened in Roslin, but much turns on the definition of embryo. I will pause there, but I should tell you that there are other layers of control within the Act. It is a sort of belt and braces approach.

Chairman: Obviously we have the Act in front of us, but we assume that it would provide in the totality a wide range of controls in law which you would be able to use on the kind of activities that go on here, but you put an important point about questioning the techniques that were applied in the Roslin Institute and we will come on to questioning on that, if we may. Anne Campbell?

Mrs Campbell

3. Mrs Deech, thank you for your opening statement. Although you made some things clear, I think you nevertheless raised a number of other questions which I think are unanswered. I know that in the Human Fertilisation and Embryology Act an embryo "means a live human embryo where fertilisation is complete" and I think this is the nub of the problem that we face. Does this mean that the cloning technique, which uses single cells and in which there is no fertilisation as such, does not produce embryos within the terms of the Act? Is that the nub of the problem in this case?

(*Mrs Deech*) Perhaps I could ask our lawyer, Graham Miles, who is in the process of drawing up instructions on that to answer.

(*Mr Miles*) There is another aspect to the definition of embryo, section 1(1)(b) of the Act, which refers to an embryo as including an egg in the process of fertilisation and for this purpose the Act says fertilisation is not complete until the appearance of a two cell zygote. So the Act, in fact, does broaden the definition of embryo to encompass that type of material. Whether or not that description is wide enough to cover the situation in the Roslin Institute is something that will be the subject of counsel's opinion when received. But it does certainly broaden out the definition from the initial one that was stated and perhaps much will depend upon whether or not the emphasis on fertilisation could be construed as being broad enough to encompass the sort of fusion of material that took place in the Roslin Institute case.

Chairman

4. Have you asked for counsel's opinion?

(*Mr Miles*) At this stage no. The intention is for a meeting with the Department of Health and there will be joint instructions on behalf of the Authority and the Department of Health as soon as possible and I am meeting with representatives immediately after this meeting.

Sir Trevor Skeet

5. This Act was passed in 1990 or thereabouts. A number of years have passed since that date. Have you not gone to the court for some guidance on the subject? Have you not tried to test it, because this is the hub of the whole thing? If you do not know what the definition of an embryo is, how can you operate? How can you grant a licence?

(*Mr Miles*) I think the situation is that one can only take a case to court if there is a case to consider in a specific instance. As I understand it, there has been no situation in the past where there has been any doubt about the scope of the meaning of the embryo as it applies to technological developments so far. This is, of course, a new situation and the Authority is responding as quickly as possible to clarify that situation.

Sir Gerard Vaughan

6. Before we go further down the detailed legal road, can I ask you a very general question indeed. Professor Jones is on record this morning as having said that ethics, which of course the law then tries to implement, will always have to follow after the scientific advances. In fact, he says, "ethics always follows science, not vice versa". This raises the whole issue of when you become aware of something that is going on, at what stage and when you feel you can step in to exercise your authority.

(*Mrs Deech*) The current project concerns animals. Our Act is exclusively concerned with humans. The current project, as I understand, was licensed by the Home Office some three years ago under a different statute. What we are discussing now is not an actuality, it is the possibility in the future, which has caused public concern, of cloning being applied to humans and, of course, as Mr Miles has said, we

[**Sir Gerard Vaughan** *Cont*]
cannot test that in the courts until and unless it happened and something went wrong. We would go through many layers of licensing before that was to be the case. On the ethical point, clearly one bears in mind public concern. Our view is that there may have been a rather extreme public reaction and now perhaps we step back and we consider the possibilities, the dangers as well as the benefits. But I would like to reassure you that under the current regime which we operate under the Act we give licences to conduct research and no licence is granted unless there has first been approval by a properly constituted ethics committee. Centres that are doing research within the NHS first have to get approval of the Local Research Ethics Committee of the relevant District Health authority. Other centres [outside the NHS] also have to refer to an ethics committee and then research projects are vetted by peers of the scientists. So that is already a concern which is catered for under existing research projects.

7. Can I just ask your role in this. Are you aware of what the different local ethical committees are deciding that they can license? Do they report to you on this?

(*Mrs Deech*) Perhaps I could ask the Chief Executive or Mr Thorne to answer.

(*Mr Thorne*) The Authority works on the basis that it will only accept a proposal for research if it is actually passed by the Local Research Ethics Committee. So that, if you like, is a gateway before it comes to us within the Authority and the licence committee for consideration. That is the first gateway and then it is a series of gateways within the Authority.

Chairman

8. I suspect what Sir Gerry Vaughan is after is who determines the ethics, is it a local committee or is it the authority?

(*Mr Thorne*) It is the local committee.

Sir Gerard Vaughan

9. This is a small group of people, is it not, who may have their own personal views? You have a national role. Are you able to override their decisions?

(*Mrs Deech*) We have an Ethics Committee within the Authority which lays down general guidelines and we have a Licensing and Fees Committee which also considers questions of licensing. So there is a central view as well as a local one, but you will appreciate, of course, that different people have

10. Who appoints your ethical committee?

(*Mrs Deech*) Within the Authority?

11. Yes.

(*Mrs Deech*) Within the Authority I, together with the Chief Executive, allocate members to the Ethics Committee. The membership changes quite frequently, so the membership of the Ethics Committee would be different year by year.

Mr Batiste

12. Am I right in understanding that the state that you have reached at the moment, as a consequence of the rapidly advancing science involved, is that you as an Authority are unhappy with the basis of your powers as they stand and will actually be seeking amendments to the rules? From what Mr Miles said, it seemed to me that although you were keeping open the option that you may have the powers in place, I thought his reply indicated very firmly that he did not think it would have the sort of powers to deal with the new techniques developed at Roslin.

(*Mr Miles*) I do not think it was a question of the powers of the Act at all, it was a question of whether or not the definition brought the matter within the powers of the Act and the purpose of seeking opinion is to be sure and certain that this type of activity is within the bounds of the Act. So it is not a situation that is clarified, but, once clarified, if there is a need for amendment of the law then we would suggest the amendment would be in relation to the definition and not any other provision of the Act.

13. By going to seek an opinion all you are going to be doing is getting a legal judgment about what the existing law really means. What we have got is a situation in which scientific techniques are advancing so rapidly and ahead of what was envisaged when this particular section of your legislation was drafted. It does seem to me that instead of trying to make the glove of the legislation fit the changing nature of the facts, what you are saying to us is that you really think that we need to look at the structure of the legislation itself, in which event an opinion about whether the definition of the embryo at the moment is adequate or not is irrelevant. What you are looking at is something so that you will not keep coming to Parliament every two or three years wanting a new change in the legislation.

(*Mr Miles*) I am not sure that that is what the Authority's view is because I think that the Authority's overall view is that the legislative framework is adequate and it is capable of meeting changing demands.

14. You are misunderstanding me. I accept that the legislative framework is adequate and we have spent a fair bit of time on this Committee looking at the legislative frameworks that have been adopted, so we are happy with that. We are talking about the definitions of the various elements of the science such as embryo. Are you taking the view as an Authority that those definitions need to be expressed in broader terms rather than the highly defined terms that we have used thus far?

(*Mr Miles*) That is certainly one aspect of it and it is certainly one matter that counsel will be asked to consider specifically, not only in relation it this particular situation but also to take account of future potential development.

Chairman

15. We are clear now, are we, that the Authority is saying that broadly the framework will stand both the test of time and indeed the practices and movements of science, but the definition certainly needs to be looked at and to be defined in law and

[**Chairman** *Cont*]
where that makes a slight shift in interpretation which is not covered then you yourselves might wish to come forward with proposals to changing the definitions within the Act which you otherwise feel is suitable to deal with these issues? That is broadly the position, is it not?

(*Mr Miles*) That is broadly the position, yes.

Dr Bray

16. The general functions of the Authority set out in section 8 of the Act do not mention the word "ethics" at all, whereas the word ethics does appear in the terms of reference of the Human Genetics Advisory Commission which was recently set up. Furthermore, Schedule 2 on licences for research sets out acceptable purposes of research and picks out particular ones such as providing advances in the treatment of infertility, increasing knowledge about the causes of congenital disease, but it does not have a general ethical reference.

(*Mrs Deech*) Are you implying, Dr Bray, that there ought to be or that it is not being done?

17. Clearly you do take ethics into account. First of all, how systemic is this considered in, for example, appointing members of the Authority with an appropriate spread of ethical backgrounds? Secondly, does it give any inhibition on the points of view from which you consider your regulatory powers?

(*Mrs Deech*) Well, there are a number of answers to this. Before I overlook it I ought to say that we have the power, and indeed have on occasions, to consult the public. We also consult the profession regularly and we take very seriously our duty to advise patients. We spend a great deal of time on giving advice to patients and encouraging them to have counselling and generally dealing with what might be called ethical concerns. Under Section 9 of the Act we have the power to set up various committees. As I have said, we do have an Ethics Committee and we take that aspect of our work very seriously. We include amongst our members not only medical people but, according to the Act, we have to have a balance of sexes. The Secretary of State also ensures that all parts of the country are represented and we do include amongst our members currently a bishop, a theologian and there have been various philosophers from time to time, all of whom are very concerned with ethical matters. I know that the word "philosopher" tends not to evoke the response that it should but all of our members do take ethical concerns very seriously. This infects our work. The Act also refers in the primary legislation to the welfare of the child, the welfare of the potential child, and the need of that child for a father. That is a fundamental basis of all the decisions that we make. I need hardly say that in the case of cloning there is no father. This statement in the Act, of course, is going to incline one against cloning. We take very seriously the welfare of the child, its psychological welfare and of course its physical welfare. We take very seriously our need to protect the public. We would never want to license any treatment that might be risky, that is the last thing that we would want and if they thought about it that is the very last thing that patients and doctors would want.

Mr Miller

18. In your opening remarks, Mrs Deech, you explained, and Spencer Batiste has developed this as well, that we are dealing with a rapidly moving science. It seems to me that the Act has tried to prohibit cloning by this multi-layered approach that you described in response to Mrs Campbell's question, on the basis of the way that scientists were thinking what was possible at the time the Act was drafted. Obviously Parliament had to take advice from the best scientific opinion that was there at the time. Given that public concern does exist would it not be better to clarify the issue in simple terms, not just for the scientifically literate, and develop an approach which prohibits the intentional artificial creation of two or more genetically identical humans, in other words deal with the outcome rather than the process?

(*Mrs Deech*) Obviously as you say, Mr Miller, it was Parliament's intention to outlaw cloning in 1990 and it used the best definition available then which I believe was lifted from the Warnock Committee. That was the state of the art then and, as you have pointed out, it has changed. We believe probably that the best way to tackle it now would be by clarifying and broadening the definition of "embryo", if it needs broadening, because by doing that you retain the subtlety of the Act and you would leave it open, were there ever to appear any positive therapeutic benefits, for a single project to be pursued. An alternative, of course, and it is for you to decide, would be to draft another section that prohibits cloning in plain language by saying "there must never be any research or treatment that would produce embryos by asexual means or that would produce two identical human beings". In other words, you could put it in plain language and that would indeed reassure the public. The down side would be that you would lose what I think is rather good about the Act, that a single project could be considered by the Secretary of State or by the HFEA however constituted at the time. I think the choice really is yours.

19. I used the phrase "intentional artificial creation of two or more genetically identical humans".

(*Mrs Deech*) Yes.

20. But you referred to the possible therapeutic benefit. Can you give any example from either the local ethics committees or from your own studies where you think there could be a possible benefit from creating two or more such humans?

(*Mrs Deech*) I will hand over to my colleague in a moment but I just want to say that I think we should all be wary of an instant reaction to perhaps very panicky publicity. I am sure that you and we would want to stand back just a little and consider because, after all, science goes on and things that seemed awful a few years ago may prove to have beneficial effects in a few years' time and we would not want to stop that, especially when we know that the rest of the world, or at least beyond Europe, is largely unregulated and what we refrain from doing they might do. My colleague, Miss Heales, can give you some examples of possible therapeutic benefits that might emerge in the future.

[**Mr Miller** *Cont*]

(*Miss Heales*) I think one of the examples that has been mentioned so far is the actual technique that was used at the Roslin may be able to overcome problems in an individual's mitochondria which is part of the genetic material but which is not contained in the nucleus as such. This may be a way of not passing on those defects to offspring. There have been other references in the media to possibly using the technique in some way to generate genetically identical tissue that can be used in a therapeutic way to treat cancer. It is not clear to the Authority yet whether these are possible now but those are some examples.

Chairman

21. I am grateful for that. The Committee fully understands and welcomes totally what Mrs Deech has said in relation to standing back and having a look and trying to reduce the level of anxiety by the fact that you are able to provide for this. We shall be meeting the MRC shortly and no doubt they will have a view on the medical aspects of this. Can I just ask one further question in relation to the definition. Section 4(3): "No person shall place sperm and eggs in a woman in any circumstances specified in regulations except in pursuance of a licence". Does this not mean that even if the definition of "embryo" may be a little deficient in so far as Mr Miles has been telling us that the HFEA still has the power to ensure that cloned eggs are not implanted in any woman?

(*Mr Miles*) I think one has to look at the fact that the word "and" is used—"sperm and eggs"—and whether or not that is intended to be used conjunctively or disjunctively. If it is the former then one still has to consider whether the situation at the Roslin Institute would be caught by that particular section. I would suggest that may be doubtful. To answer that slightly more fully, there is a control within Section 4(1)(b) of the Act which actually would catch the specific situation at the Roslin Institute because in that case there was a donor sheep that provided the egg that was used. That would be caught by the provisions of Section 4(1)(b) so that procedure would not be able to proceed without a licence.

Dr Bray

22. Mrs Deech, you quite rightly argued for not making any hasty decisions but, on the other hand, it is only in the context of a public debate that long-term guidance gets sufficiently high in the public agenda to give real guidance to research scientists who are looking a very long way ahead, shaping their own plans and projects to match. Therefore, is it not likely that to deal with the concerns as much of research scientists as of the public that a combination of measures will be needed from total prohibition to definitions to regulatory powers and therefore you may well have a need to include in Section 3(2) "no person can place in a woman a live embryo cloned from any source" or something like that but then you will be in problems with the definition of "cloning"? You do seem to be slightly setting your mind against further prohibition. Is it not likely that the public will require that a future Parliament legislates some further prohibition?

(*Mrs Deech*) If I can say two things in response to that. We believe there is a bit of time in which nothing can happen that might cause public concern in at least the next few months, maybe longer. It took nearly 400 attempts to produce Dolly. No-one has really tried to do this to a human yet and we do not believe that this is happening immediately. That gives you time. The second point is that it is, of course, ultimately for Parliament to decide. The HFEA will of course carry out and regulate as Parliament decides. It may very well be that your assessment of the public mood and your own concerns are such that you wish for a total prohibition in broad terms and that would be the end of the matter. Our view, and of course it is just our view, is that those concerns could be equally met by clarifying and, if necessary, broadening the definition of "embryo". This is ultimately a decision for you as guardians of the democratic wellbeing and we will obviously carry out and advise you following on your decision.

23. That would give you powers to regulate. The public might wish to be assured that you will in fact use those powers, in other words that it becomes an outright prohibition.

(*Mrs Deech*) There is a way to do that if once we clarify the definitions of "embryo" "gamete" and "fertilisation" the Secretary of State is given direct powers in the Act to make regulations under the Act which could prohibit certain types of work.

Sir Trevor Skeet

24. Mrs Deech, I want to pursue just one point very, very briefly with you. You have been talking now on two occasions about a broadening of the definition of "embryo". This could prove to be very restrictive on science. Would this not be detrimental?

(*Mrs Deech*) Well, as I have said, I think one can take care of the public concerns but also consider science project by project by project through our licensing system. I think it is for parliamentarians to decide whether the public concerns are so great that there must be a total blanket prohibition or whether they wish to continue with the existing system. In our view we think the flexible approach when drawing up amendments is a good thing. That is our view but, of course, you are the ones who have the power and the duty to decide that.

25. On the other hand you will be advising Parliament.

(*Mrs Deech*) Yes.

26. And you did say in your introductory remarks that you want to adopt a flexible approach. Have you in mind a system for the United Kingdom or the more open system of the United States?

(*Mrs Deech*) We have not considered the system in the United States in detail although I do have information on Europe. Clearly things may go on in the United States which we would not want to happen here and because of the ease of mobility and exchange of scientists we quite accept that scientists may go abroad and do things that they would not be allowed to do here. We are all in favour of scientific

[**Sir Trevor Skeet** *Cont*]
progress but we have a problem which relates to our position within the European Community. Across Europe there are different standards in different countries. For example in Germany, I suppose because of its history, there is a total prohibition on this sort of research. In Italy anything goes, there is a *laissez faire* approach. Norway does not allow embryo research. In France the creation of embryos for research is banned and so on. Every country does something different. The problem is this: although Europe is working towards it there is no pan-European approach and, as you will know if you followed the details of the Diane Blood case, we are now aware that there is a very strong European right arising under the Treaty of Rome for citizens of this country, citizens of any European Union country, to travel abroad freely in search of medical services. That right can be outweighed but only by the strongest public policy reasons in this country. I therefore suggest to you that you ought to consider this because let us imagine in a few years' time that although cloning of various types is illegal nevertheless somehow it arises that there is a cloned embryo and the newspapers get the story, there is this pretty little baby, the baby needs something or other and it is forbidden in this country, I imagine there will be pressure to allow the patient to go abroad some place, to Europe or America, where there are no controls. That is not something we can do anything about. I would suggest to you that territoriality is something that must be considered in drafting new statutes, new amendments, on this topic. We are effectively at the mercy of lower standards abroad.

Chairman: Thank you for that. That is very important advice.

Mr Batiste

27. I am still trying to weigh up the structure of what ideally we should have in place here to cope with the future. I think all of us would share your view that to enshrine the regulation of a rapidly moving science in primary legislation that can only be changed with difficulty is not very desirable. The flexibility of your licensing system is obviously an attractive way of dealing with it provided the public is satisfied. You have suggested an interim step between those two and the intervention of the Secretary of State. Do you think that the new Human Genetics Advisory Commission will have a role in this in advising the Secretary of State to give directions to you as to the ethical judgments you should make in your licensing?

(*Mrs Deech*) That might well be the case. There is a plethora of committees in this area. We are glad to note that the new Chairman of the Human Genetics Advisory Commission is Sir Colin Campbell who was my predecessor at the HFEA and he is, therefore, very well acquainted with the problems that we face. I do believe that that Commission, under his guidance, will be well placed to give such advice. However, and Mr Miles will correct me if I am wrong, the Secretary of State can only make regulations that are within the purview of the Act. The regulation making power cannot go broader than the Act itself.

28. But it would help define ethical considerations that you might have to take into account, that would be within the purview?

(*Mrs Deech*) We would like to keep to ourselves the ethical duties that we have but we are glad to know that there is a Human Genetics Advisory Commission under that particular leadership.

29. Given that that structure is in place and that seems to be a pretty sensible structure, do you not think that we have got a case for including all research using human gametes within the purview of your committee and then avoiding problems of definitions which arise subsequently?

(*Mrs Deech*) We have a problem there. It might well be desirable but, however, much of the research carried out on gametes will not be of great interest to the public and does not involve their genetic component or the creation of embryos, for example research on the storage of eggs. More seriously we are a lean and economic Authority. Our hands are full doing the work that we do. If you were to decide that all research on gametes should be licensed this would dramatically increase the work of the Authority and it would require a significant increase in staff and resources. That is a decision for you to make. However, we would welcome discussion on the possibility of regulating research projects of the sort that are of concern today, the sort that require the manipulation of the genetic component of gametes. It does not follow that this should be done solely by the Authority. In other words, this is all worth considering. We are a very economic, heavily pressured Authority. We would not be able to take on more with our current staffing and funding. I am not saying that we should not or we would not but it would require a commitment of resources.

30. Can I just probe that a little bit further if I may. Clearly as you operate at the moment you go on a case by case licence so people come to you with projects, you examine those projects and you license them. If you were to go downstream, as it were, and to take on the overall supervision of a wider range of activity, much of which would not be of the same urgency and importance to examine on an individual basis, would it not be practicable to operate blanket licences for certain kinds of research which would not be terribly onerous?

(*Mr Thorne*) I am not sure that the Authority would necessarily go down that route or it would be very sensible. I think blanket cover is a bit of a blunt weapon. I think somebody should look at each project as it comes up. I think that is a far stronger way of going about things.

Mr Bruce

31. Can I ask you Mrs Deech, or any of your colleagues, perhaps looking at this from a different direction. Currently under the 1990 Act is it prohibited to interfere with an embryo? Let me give you an example which seems to be moving in this direction. A man and woman, husband and wife, one of them has an inherited genetic disease which they are likely to pass on to their children. Is it legal now for a scientist to effectively take the embryo which is going to go to term and try to repair the genetic

[**Mr Bruce** *Cont*]
make-up of that particular egg and reimplant it? If it is illegal to do that, should we not in reviewing the Act also be reviewing things that would be acceptable to the public morally such as doing repairs to genetic material as opposed to enhancements to genetic material or cloning them?

(*Mr Thorne*) That is a very complex question. Can you put it in context again. You are saying you start with a couple?

32. A couple who are married. They want to have a child, an in vitro fertilised embryo, let us say, as opposed to removing it from the mother, and it is repaired before being implanted in the mother to try to solve the problem of the genetic disease. For example, I have a constituent, I mentioned this on TV yesterday and I mentioned it to this Committee, who has Anderson-Fabry disease. There are a lot conditions where it has been identified that there is a genetic problem which is being passed on generation to generation.

(*Mr Thorne*) This is pre-implantation diagnosis and I wanted to make sure there was not something hidden in there that I missed. That actually goes on at the moment.

33. I am not talking about diagnosis and saying, "I am not going to implant it." I am saying is it currently legal to repair or to interfere with that embryo?

(*Mr Thorne*) Yes it would be. Certainly within the Code of Practice it would be because I know of, somebody can correct me, occasions when it is done and it is prohibited in the Code of Practice to modify eggs or embryos without actually the necessary research having been done first on the outcome of it. So as things stand at the moment there is protection against that.

34. I am sorry there are some negatives in there. Protection against it being done?

(*Mr Thorne*) Against it being done.

(*Mr Miles*) Can I draw specific attention to one part of Schedule 2 to the Act which requires the Authority to consider certain matters before granting a licence and Schedule 2, paragraph 1(4) says: "A licence under this paragraph cannot authorise altering the genetic structure of any cell while it forms part of an embryo." That may well cover the situation.

35. It is illegal, can we get this clarified, under the present Act? The second part of the question therefore is if this is seen ethically as the correct thing to do in the future, should we be looking again at the Act?

(*Mr Miles*) If my interpretation of your situation is correct, it would be prohibited at the moment for the Authority to issue a licence covering that type of activity.

Mr Vaughan

36. How concerned are you over the implications of the Roslin cloning and do you think any major changes in the regulatory system are required to deal with it? Are you very concerned at the implications of this and can you deal with them?

(*Mrs Deech*) We are concerned, as I think most members of the public are, about the possible ignoring of the individuality and value of each human being as an entity in himself or herself. I think we all feel that the manufacture of human beings to serve other people's ends must be a bad thing, to grow them to provide a consolation or to provide skin or bone marrow does not seem to us to be a good thing and I believe that view is widely shared. On the other hand, because we are mixing with scientists we do understand that within careful parameters there may be research in the future from an early stage of this process that might be of benefit to mankind and we wish, together with you, to find a way forward that produces benefits to mankind but steers well clear of the artificial production of identical human beings without a father as it were at all, simply to suit somebody else's ends. By pure chance I met a gentleman yesterday on a television programme who told me he had received phone calls from all over the world on this topic. For example, a woman had telephoned him to say that she longed to hold her aged father in her arms again and that she would like to clone him and carry him herself as an egg implanted in her. This I thought was quite horrendous although he seemed to think it was not. I imagine that public reaction to that would be that this is really quite beyond the bounds of acceptability and we do not think the public should be misled into thinking that anything and everything is possible and desirable because of modern scientific developments; it is not.

37. Do you have the legal framework at the moment to deal with the problems that are likely to come up?

(*Mrs Deech*) We are 100 per cent convinced that we have the legal framework to deal with everything except the one technique that the Roslin Institute carried out and reported last week if it were to be applied to humans. We know there will be a gap of time before that happens. We expect within weeks rather than months to receive advice from counsel on the definition of embryo, fertilisation and gametes in this new atmosphere and then we will be able to give firm advice to you as to whether this Act needs amendment of the definitions or something broader.

Mr Miller

38. Coming back to the point that I put to you earlier on, whilst I think all in the Committee would accept that there are areas of research on embryos which are desperately important in terms of our understanding of some conditions and indeed the curing of some conditions, there are, nevertheless, some outputs that we would all find extremely difficult to live with. Would it not be possible to ease the public's concern by defining the output, the actual final creation of the cloned human being as an illegal act?

(*Mrs Deech*) As I have said, this could be done. It would reassure the public.

39. That could be done without damaging the kind of research your colleague spoke about earlier on?

(*Mrs Deech*) I am not sure it could. If there was another section that said you must not produce identical human beings through asexual cloning—I

[**Mr Miller** *Cont*]
am not drafting but you know what I mean—I think that would take precedence over everything else, it would blanket and stop—

40. With the right definition of embryo, it would be possible?

(*Mrs Deech*) That is an alternative. You do not need both. Either you put in a blanket prohibition, the drawback being you will probably have to come back to the Act every few years and change it or you broaden the definition of embryo and that would keep us going for the foreseeable future and enable us to control project by project anything that the scientist put there.

Chairman

41. You raised the issue of different legal systems applying in other European countries, some hugely flexible, some completely exclusive. Do you think there is a role for European law in this to try and standardise the law in this extremely sensitive field?

(*Mrs Deech*) Yes we do. We would welcome a European law. However, there are drawbacks. It will take a long time and because it will be a consensus law it is going to be very vague in precisely those areas that we are concerned about. It will also permit individual countries to derogate from individual sections. For example, there is already a convention on human rights and bio-medicine due for signing by Member States this April. This Convention does not have the power of a Directive and only applies to the Member States who ratify it and of course there will always be those who do not. Article 18 of it prohibits the creation of embryos for research purposes but that is something we allow sometimes in this country. It also states that where research on a human embryo is permitted by a state adequate protection should be given to the embryo. That we do. A protocol concerning the protection of the embryo and the foetus is currently being produced by the Council. Questions as to the Government's attitude on this should be directed to the Department of Health. They can give you their response to this Convention, but I think from what I have said already it is apparent that it is not really detailed enough. It does not, as far as I know, deal with cloning and individual states may derogate from this so it is not wholly satisfactory. We would welcome, if it were possible, European-wide standards on IVF treatment never mind cloning.

42. That of course might not be a matter for an Act but purely some kind of Directive in relation to practice?

(*Mrs Deech*) But we do not see it coming in the near future.

Mrs Campbell

43. Mrs Deech, the work of Roslin could either be regarded as an amazing scientific advance, which I think it is, or I can imagine one reaction is that this has all landed us in a pretty pickle and we should avoid this situation if possible in future. I wonder if you feel that the regime that has been established for human research should be extended to research in animals?

(*Mrs Deech*) That is dealt with, I believe, by the Home Office.

Chairman

44. Currently.

(*Mrs Deech*) We deal with the human embryo. In our Act there are prohibitions on mixing humans and animals. Animals are not really under our remit. There is an Act, the title of which escapes me, from 1986 dealt with by the Home Office and I think it is for the Home Office to explain to you their attitude on these matters. We are strictly confined to humans.

Dr Bray

45. It is possible to inject human genes into animal gametes or embryos or organisms. That is surely another example of the way, once you get any set definition, research is going to slide away from you.

(*Mrs Deech*) Of course you are right.

46. It is a bit uncomfortable to have you saying that the legislation is all fine except in the case of a particular thing that happened.

(*Mrs Deech*) As far as animals are concerned, there are direct prohibitions in Section 3. The placing of an embryo in any animal is forbidden under our Act and "no person shall place in a woman a live embryo other than a human embryo" and the same applies to gametes and mixing is forbidden so anything of that nature is forbidden under our Act. Although I do not know it, I imagine our Act has to be read in conjunction with those under the Home Office rules that concern animals.

47. The whole purpose of the Roslin project is to produce proteins which are an expression of human genes implanted in sheep.

(*Mrs Deech*) As far as further research on animals goes, I do not think it is for us to give you the information. I think that would be for the Home Office to elucidate.

48. I simply make the point if you put a gene or if you cannot put an embryo, there is a huge spectrum in between.

(*Mrs Deech*) I think that strengthens the argument we put forward that we should be a little flexible because there may well be advances in the future that we should cope with.

49. This is really a general point on how specific the research licences need to be. They do refer to a particular procedure, a particular person, particular premises. Do you have powers to make them broader than that?

(*Mr Thorne*) They refer to a person and premises but we in fact have the laboratory protocols that will be used and an enormous amount of detail and we receive information back so a great deal is, in fact, known about that work.

Mr Batiste

50. How frequently do you refuse requests for a licence?

(*Mr Thorne*) In research or in treatment?

51. Across the range of your activities?

[**Mr Batiste** *Cont*]

(*Mr Thorne*) Probably initial refusals run at five per cent. Then they could come back. A Licence can be offered subject to conditions and you might go back to a licence committee, and once the new conditions have been accepted, the project would go through. But Research Licences, certainly they can be offered with conditions attached which the centre might not accept. If that was the case, they will not do the work.

(*Mrs Deech*) They are also renewed every year and reports are required on how that research is going and all clinics and research centres are inspected.

52. What would be the kind of reasons why you would reject without being too specific obviously because that would be wrong. If you reject a licence it may be that with conditions it can be brought in, as you describe. How often do you get applications for research which you feel to be wholly unethical and should not proceed?

(*Mr Thorne*) In the time I have been with the Authority, three years, I do not know of a situation where that has happened because I think the scientists out there understand what the set of rules is but certainly ethical issues have been raised when looking at research applications regarding things like consent because you have to have information which the patient looks at when they consent to the use of their genetic material effectively and the Authority has insisted that information be changed and the patient is better informed about what is happening.

53. You quite often would be involved at a much earlier stage than an application for a licence. People would approach you to see whether the lines they are thinking about would be acceptable if ultimately they came to you for a licence?

(*Mr Thorne*) Yes.

Chairman

54. Could you give us some idea of the volume of requests for licences which you deal with in a year.

(*Mr Thorne*) The Authority works on a rolling year annual basis so for licence renewals there will be something like 127 treatment licence renewals in a year.

55. Each year it has to be renewed?

(*Mr Thorne*) Yes and 25 research licences are also looked at annually and of course there are centres coming in and dropping out of the system as well.

56. New applications as opposed to renewals?

(*Mr Thorne*) New applications as opposed to renewals. Research, probably four a year, I am sorry I cannot be more exact; treatment centres probably eight.

(*Mrs Deech*) In our annual report—

57. We have the figures.

(*Mrs Deech*) There is a list of current research projects.

Chairman: It is good to hear that the volume is not all that great and that the detailed requirement is obviously there.

Mr Miller

58. To pursue the inspection issue a little bit more. Are inspections conducted unannounced? If so, at what level do those inspections take place and, finally, do you envisage having the same sort of problem that Bill Clinton appears to have, according to *The Independent* this morning, quoted alongside Jeremy Bray I notice, that he is having difficulty establishing one set of rules for publicly-funded laboratories and another for privately-funded ones.

(*Mr Thorne*) In response to the last question, no, they are all treated exactly the same way. In relation to the first one, yes, we do carry out unannounced inspections.

59. Is that with a scientific team?

(*Mr Thorne*) It will be geared according to what the perceived problem is.

60. Looking at paperwork or the inspection of laboratories?

(*Mr Thorne*) Both.

Sir Trevor Skeet

61. Just one simple point. I see you have got a very impressive list of inspectors, some 54 in total. How do they qualify for this? You obviously make your own selections but what are the criteria you use?

(*Mr Thorne*) For the last recruitment of inspectors, the initial trawl was done amongst the royal colleges, FRCOG type people. The Association of Clinical Embryologists was asked to submit names, individuals could submit names and people could submit their own names. From that there was a committee of the Authority, which was a subset of the Licensing and Fees Committee, set up, which looked at all the applications and made their decisions on that basis.

62. And you keep them for a term of years?

(*Mr Thorne*) We keep them for a term of years but they are turned over.

63. And they are turned over every—

(*Mr Thorne*) We change our blood (if I can put it that way).

Chairman

64. Mr Thorne, have you ever withdrawn or revoked a licence to conduct research? You have a roll-over annual renewal?

(*Mr Thorne*) We have never, to my knowledge, revoked a research licence but people have, in fact, given up doing research.

65. So there has not been a case where you can say, "We withdrew this licence or cancelled this licence on certain grounds"?

(*Mrs Deech*) I actually recall not so long ago an on-going research project where we felt that too many embryos were being used, we thought for no good reason, and we went back to ask further questions and I think the project did stop. I do assure you that we keep a careful eye on these things and that the opinion of eminent peers of those scientists are sought year by year.

[**Chairman** *Cont*]

66. So we deduce from that that obviously you keep as close an eye as you can, that you would regard revocation as a position of last resort but would prefer to see the work conducted in a different way or to be more defended? The use of embryos is clearly a point of concern to you?

(*Mrs Deech*) There are two types of revocation. I do not want to confuse them. The majority of our work is to do with the licensing of IVF centres, which are inspected every year, and there have been revocations and that becomes quite a serious legal matter because usually the person responsible for the clinic will want to challenge this by appealing to the Authority or in court. It is rare but it does happen. As far as research goes, I think revocation is not quite so common because if we check up on the research, there is an application for renewal and questions are asked about it, that is taken as a signal by the researchers that it will not be renewed unless they justify what they are doing, change what they are doing or abandon the project. It does not normally come to that but this is something that we know we can do and, in my experience—and I have been Chairman for over two years—we certainly have done it in relation to IVF centres.

Mr Miller

67. In terms of public perceptions of your activities, we see on some occasions that some of the newspapers have painted you as the bad factor in the equation, as in the Mrs Blood case, and in other cases you have been seen as the saviour of ethical standards in this field. Do you think that the public are adequately informed about your activities, do they understand the role of the Authority, and given a wish-list, what would be on your wish-list to help aid that public understanding of what is a very complicated field?

(*Mrs Deech*) Let me work backwards. Within our very limited budget we issue leaflets, we issue a Patients' Guide to IVF treatment, we hold conferences, we try and do our best with public relations. We wish we could do more but our budget is very stretched. We are the same size as we were five or six years ago, and yes, of course the number of treatments, the number of patients being treated, has escalated and what we have found in the last two years, or perhaps one year, is that public awareness has grown. When I took over as Chairman I was assured that it would all be really quite quiet and I have found in the last year that the HFEA has gone through its initial birth pangs, as it were, of setting-up the Code of Practice and regulating clinics, and issues that were brewing but quiet a few years ago have now come to the surface. We have now found immense public awareness arising from cloning, arising from the storage of frozen embryos, arising from the Mrs Blood case. We are very well aware of the public interest in our work. We would dearly like to do more. We are simply not sufficiently budgeted in order to do that. Our budget goes almost entirely on maintaining our database and doing our core statutory duties. We only wish we could do more. We understand public feelings about us. We see ourselves perhaps as the thin blue line standing between public concerns and scientific progress. We are very conscious, as I hope you have seen today, of the need to balance the two. We found the Mrs Blood episode painful but we really do believe that the law must be upheld and we are most gratified that the Court of Appeal has confirmed our interpretation of the law that written consent is necessary. We do not wish for a system whereby people's wishes are ignored or trampled on. We do not wish for a system whereby human bodies are treated as banks of some sort without discovering what their wishes are. We respect human dignity and autonomy and that is what lay at the heart of the Blood case and, painful though it is, we remain convinced that we did the right thing. We become aware of the danger of what I might call media-led campaigns, whether it is panic over cloning or whether it is sympathy for a woman or a baby who look attractive in the press. We are aware of that danger. We hope that Parliament will understand the increased public role we have and we hope that the officials, if necessary, will give us the means to carry out what is a new and bigger job and quite different from what it was a few years ago.

Chairman: That is a very fine summing-up of your position and the way in which, if I may say so, you have chaired and developed your chairmanship in an extremely effective way. The Committee is gratified. There is one further question from Dr Bray.

Dr Bray

68. We quite appreciate the difficulty within a limited budget of dealing adequately with the public information function you have but I am sure you recognise that any public information efforts you make will be dwarfed by the huge volume of press and media interest and by, likewise, debate and research within the scientific community. Do you feel there is a need in a sense to swim with the tide and that you need to respond to public opinion?

(*Mrs Deech*) We do this through the process of consultation. We meet with scientists all the time, with the royal colleges, to ascertain their opinion. We sometimes appreciate the amount of scientific information put out in the press. We think the explanation of something like cloning is actually quite well put in the serious newspapers, although the conclusions drawn may not be ones we agree with, and we are grateful for that. We put out videos, we put out leaflets, we have conferences; we do all we can within our budget both to give and to receive opinions, to be informed and to give information. Many of our membership are world-class scientists, for example Dame Anne McLaren, and we rely very much on them to keep us up-to-date. They go to conferences, we go to conferences. We do all we can within our budget to keep up-to-date.

Chairman

69. Thank you. Thank you and your team for coming and answering the questions and providing us at this short notice with a very clear steer in some directions, not entirely exclusive of the need for further public study of the immensely enhanced role that you clearly play. Thank you very much.

(*Mrs Deech*) Thank you, Sir Giles.

THURSDAY 6 MARCH 1997

Members present:

Sir Giles Shaw, in the Chair

Mr Spencer Batiste
Dr Jeremy Bray
Mrs Anne Campbell
Dr Lynne Jones
Mr Andrew Miller
Sir Gerard Vaughan
Dr Alan Williams

Memorandum submitted by the Roslin Institute and PPL Therapeutics Ltd (5 March 1997) (CLE 1)

NUCLEAR TRANSFER FROM CULTURED CELLS IN SHEEP

Background

Roslin Institute (Edinburgh) is sponsored by the BBSRC and is a Company Limited by Guarantee and Scottish Charity. The role of the Institute is to conduct basic and strategic research to create new opportunities for the livestock products and animal biotechnology industries; in addition the Institute carries out research in animal welfare both to inform Government policy and address public concerns. Its funding comes as a BBSRC Competitive Strategic Grant (19 per cent) MAFF Commissions (35 per cent) and contracts from various public and private sources (46 per cent).

PPL was initially founded in 1987 to commercialise the transgenic technology developed at Roslin. It has its headquarters/main laboratories on the Roslin site with subsidiaries in Virginia, USA and New Zealand; the Company was floated on 11 June 1996 with a valuation of over £100 million.

The Committee's Questions

1. *The way the experiment was approved*

There are no specific regulations governing nuclear transfer from cultured cells. The research is, however, covered by general regulation controlling scientific procedures, animal welfare and genetic modification.

(a) Animals (Scientific Procedures) Act 1986. All of the research on nuclear transfer was carried out under the Animals (Scientific Procedures) Act 1986. The proposed research on nuclear transfer was approved in Project Licence 60/00645 Embryo development and manipulation which was granted on 1 June 1989 and subsequently on Licence 60/1688 Embryo development and multiplication which was granted on 21 June 1994.

The objectives of the research were to establish methods for the introduction of precise genetic change in livestock species and for multiplication of embryos.

(b) Roslin Institute Animal Experiments and Welfare Committee. Research projects are reviewed by a committee which includes "lay" members of staff, a statistician and scientists working with animals. The nuclear transfer project was reviewed on 9 July 1994 and 26 May 1996.

(c) Advisory Committee on Genetic Modification (HSE). Work with transgenic animals is covered in guidelines issued by ACGM (ACGM/HSE Note 9). The Institute is registered with the HSE for work on genetic modification and has a Genetic Modification Safety Committee. All experiments are Group 1 type A which only require local prior risk assessment and annual retrospective notification to HSE. None of the research so far published involved genetic modification although new experiments are in progress in this area; a risk assessment has been made and they are Group 1 type A.

2. *The likely applications of the research in the short to medium term*

(a) Biomedical Applications

PPL Therapeutics specialises in the production of therapeutic proteins in the milk of transgenic livestock because it appears that, for some proteins, this route of manufacture offers the only cost effective method. This involves the injection of a human gene into a fertilised livestock embryo. This "conventional" technology is robust but limited in the following characteristics:

(i) Only a small proportion of animals generated carry the new genes (< 10 per cent).

(ii) Of these, most do not express the human gene in milk at commercially acceptable levels.

(iii) Genes can be added but not removed.

In order to address these deficiencies, PPL and many other companies and academic groups had for some years been looking for an alternative technology akin to the ES technology developed for mice. Unfortunately this research has so far proved fruitless. However the rather different, nuclear transfer technology developed originally by the Roslin Institute and utilised in the recent work of PPL together with Roslin presents not only a solution to the above shortcomings but also because of the cloning aspects allows further biomedical benefits as detailed below:

(i) All animals born will be transgenic.

(ii) Because of the success with adult mammary cells (remember these are the cells which make milk), we should be able to screen genetically modified cells in the laboratory for high expression before making the animals.

(iii) This raises the prospect of not only making exclusively, high expressing animals but also making "instant" ie first generation production flocks/herds. This could reduce the time to patient the drugs developed by this route by several years.

(iv) We should be able to remove specific genes from the animals.

Realistic targets and objectives include:

(i) The PrP gene which is implicated in scrapie (sheep) and BSE (cattle). This would provide a unique research tool with which to research the pathology and cause of the spongiform encephalopathies.

(ii) The betalactoglobulin gene in cows. This gene product is believed to be the major allergen in cow milk.

(iii) The gene responsible for coating pig organs with alpha 1-3 galactose. This sugar coating leads to severe rejection problems when human blood comes into contact with pig tissue.

(iv) Animal models could be provided for congenital and other examples of severe human disease.

(b) Animal Breeding Applications

Nuclear transfer from cultured cells taken from adult animals is likely to be of use in livestock breeding. To make use of the technology in this area we will first have to adapt it to cattle and pigs; we do not know how easy or difficult this will be. Cloning would be used by the breeding industry to bring the level of the general herd up to the level of the elite breeding populations. The control of genetic diversity of animal populations is well understood due to the widespread use of artificial insemination and strategies to both incorporate cloning into breeding schemes and maintain diversity are feasible.

FUNDING

The project at Roslin Institute is currently funded 65 per cent by the Ministry of Agriculture, Fisheries and Food; the rest of the funding comes from BBSRC, EC and industry. MAFF have indicated that they will terminate 50 per cent of their funding on 1 April 1997 and the remaining 50 per cent by 1 April 1998.

Examination of Witnesses

PROFESSOR GRAHAME BULFIELD, Director and Chief Executive, Roslin Institute, DR ALAN COLMAN, Research Director, PPL Therapeutics, DR IAN WILMUT, Roslin Institute, examined.

Chairman

70. Professor Bulfield and your colleagues, Dr Wilmut and Dr Colman, you are most welcome. May I say that with all the considerable pressures on your time you have responded swiftly and generously in coming to this Committee so that we can ask you some questions on the astounding work that you are doing at Roslin. You can see our team identified before you. We can see your good selves. Would you wish to make a statement or an introduction of some kind?

(*Professor Bulfield*) Not a statement, Chairman, but if I may just introduce us and say where we are coming from. I am Grahame Bulfield, the Director and Chief Executive of the Roslin Institute. Ian Wilmut is a Principal Investigator of the Roslin Institute. It is in his laboratory that the nuclear transfer work with sheep started.

71. He is described as an investigator, is he?

(*Professor Bulfield*) A Principal Investigator, which is a Senior Scientist in the Institute. He will answer any technical questions you may have on the procedures. Dr Alan Colman, who is on my left, is Research Director of PPL Therapeutics, who have a licence to exploit the work in their field of use and he will answer any questions you may have about the use in the biomedical industry. I will take any questions you have about use in the agriculture industry or any more general questions.

72. Very good. As you would expect, we have a range of questions and in a sense we can rely on you to farm them to your colleagues as you wish, but we

[**Chairman** *Cont*]
have one or two which would be directly to the two people on your left and right. I will start with a general question. What scientific challenges prompted you to conduct this particular experiment?

(*Professor Bulfield*) I think I will pass that one over straightaway to Dr Wilmut.

(*Dr Wilmut*) I think it is important to recognise that this is a programme of work which has been running for about ten years and the stated aims in all of the documentation would have been to develop methods for the introduction of precise genetic changes in livestock and for the production of embryos. Our original strategy was to do this with cells derived from embryos because there is a well-established system in mice which allows the targeted change of genes in that species. Over the years, despite a lot of effort not only in our Institute but elsewhere, it has not proved possible to replicate the embryonic stem cell system in any other species and so we naturally moved on to use cells of a variety of different kinds as a source of the genetic material, starting with the rather later embryo stages, which we used in the experiment which led to the birth of Megan and Morag who were introduced to you a year ago, and then in an assessment of the power of the new nuclear transfer technology, to ask if the success was a reflection of the nuclear transfer or of that particular population of cells. With our collaborators we set up a study of a different population of embryo cells, cells from the fetus and cells from an adult, in order to ask that very general biological question.

73. What new avenues does this science open up?

(*Dr Wilmut*) If I may, I would suggest that that overlooks the fact that we have probably achieved our original objective in that until now the only way of adding genes to livestock has been a relatively primitive one, it has been used by a variety of people for research and commercially by companies like PPL Therapeutics, but we are now confidently looking forward to the time when we can make targeted changes in sheep, probably in cattle and also in pigs. So the initial advantages stem from that new opportunity. That has a great range of applications in research and industry. I do not know if you would like me to enlarge on that.

74. Your opinion on how things can develop from there would certainly be interesting.

(*Dr Wilmut*) When you are describing a new breakthrough like this it is always very difficult to get a balance right in that it is very interesting and encouraging that we have been able to obtain offspring with this variety of different cells, but you have to put into the balance the fact that the procedure was very inefficient. In the case of the adult cells, we had one lamb derived from 277 reconstructed embryos and 29 of those were judged to be suitable for transferring to recipients. So one of the aspects of the research which we would wish to continue would be to try to improve that so that a greater proportion of the embryos will become offspring. We do wish to extend this to other issues. There will be a commercial application that perhaps Alan is the best person to describe. In terms of research, there are opportunities to study genetic diseases, both of livestock and of humans, and some very basic biological questions in relation to differentiation and aging. I am quite clear that we have not yet identified all of the new questions. The observation is so new that we are having new suggestions put to us almost every day.

Chairman: I think we will come to PPL a little later, if we may.

Dr Bray

75. *Nature* in its news and views report of your letter said, "the results are of profound significance. Not only do they confirm that the genome (with the exception of the immunoglobulin and T-cell-receptor genes) does not undergo irreversible modifications, but they will open up a range of new ways to think about questions that are of current interest ..." John Gurdon in a letter to the Committee said that "his work had not succeeded in generating a normal adult animal in a nuclei of cells of an animal". Would you say that that was the underlying achievement?

(*Dr Wilmut*) Absolutely. I drew very heavily on the textbook that Professor Gurdon published some 20 years or so ago, in which he offered as a tentative hypothesis that there was no irreversible genetic change and that was the conclusion at the end of his book. We have simply demonstrated that.

76. What do you think *Nature* had in mind when it said "a range of new ways to think about questions that are of current interest"? You have already mentioned some.

(*Dr Wilmut*) There is one that we mentioned in the paper, the question of aging, where, put very naively, the ewe from which the cell was taken was six years old, Dolly herself is now six months old, approximately, is she in any sense $6\frac{1}{2}$ years old? There are questions that can be asked about the change in molecules within the cell to give us some indication of that by making a comparison between the aging length in the lamb and in the cells. That will give us an observation. I have to say, I am rather nervous about any experiment with an N of 1 with one observation, but, nonetheless, we could do that.

Dr Jones

77. Is it only one? You have not repeated it again at all?

(*Dr Wilmut*) No. Can I be quite clear, we have not tried. It is not that we have tried and failed. Everything that we have done with an adult cell is described in that manuscript.

78. Why have you not tried if you are nervous about an N of 1?

(*Dr Wilmut*) Until now the aging question has not been a priority. I am speaking for myself here because even within the Institute there would be slightly different priorities and enthusiasms.

79. I do not mean the aging question. You might never repeat it again.

(*Dr Wilmut*) I think that is right. To us the opportunities to use the techniques perhaps with foetal cells are what is exciting. To me that is an exciting opportunity, that is what we have begun to focus on as the next stage. As part of the discussions

[**Dr Jones** *Cont*]
of the last fortnight I have recognised that there are a lot of other questions, but we have not started to address those yet.

(*Professor Bulfield*) Chairman, I think we should be clear about this point. There were eight lambs born, four of which were from an embryo cell line and three were from a foetal fibroblast cell line, which is a differentiated cell, and one from an adult cell line, so from our point of view that was also exciting. We can only do these experiments once a year because sheep only breed once a year and Megan and Morag were produced in last year's cycle of experiments and these were done in this cycle. Our main aim was not to do this but to enable us to have a cell line we could genetically modify in culture and then transfer the nuclei back. In many ways the fibroblast line is just as interesting and is also a proof of the general hypothesis that Ian talked about just then, that the nuclei are not irreversibly differentiated.

Mr Batiste

80. A lot of the public debate since all this was made public has been at the sort of level of Frankenstein unchanged. I do not know which of the three of you would be best to do this, but I wonder if you would like to put on record the practical benefits that could flow from the discoveries that you have made across the medical range?

(*Professor Bulfield*) We see two areas of benefit, one medical and one agricultural. I will pass over to my colleague, Alan Colman, to talk about the medical and then, if I may, I will deal with the agricultural.

(*Dr Colman*) It is nice to see some of the Members of the Committee again. The last time I saw you I was singing the praises of the most famous sheep in the world, Tracy, who has now been eclipsed by Dolly. We got into the work because, as I have outlined in a memorandum, at the moment we make therapeutic proteins for medical use in the milk of transgenic sheep and cattle, a lot of the latter work being in the US. There are limitations in the present technology where, for example, most of the animals born to the technology we use presently are not transgenic so there is a large waste in the use of animals. Many of those transgenic animals which are born do not express the protein of medical interest at sufficient levels to make anyone commercially interested. The other major dis-benefit of the present technology is there is an inability to remove genes. You can add genes but you cannot remove genes. So our interest started primarily with the need to remove genes and the technology we worked on for some years, and my colleague has mentioned it, failed and has failed in all livestock. Nuclear transfer technology has not only brought forward the possibility of removing genes but it has the bonus of cloning. The benefits I see from this technology and some of the examples I have given in a memorandum are, for example, using the mammary cell line that we provided for this experiment. By genetically manipulating it we should be able to get a read out of the expression of a human protein of interest long before an animal is made. So our view is that we can add a particular gene to the mammary gland cells and then select a cell which is giving very large levels of this protein with the reasonable anticipation that if we make that cell into an animal that animal will be a very high producer of the protein.

81. You mentioned Tracy and the protein that flowed from that. In terms of translating what you are doing into terms that the public would understand as a benefit that they would perceive, could you please bridge from the technology that you have just described to the consequences of the technology in terms of public benefit?

(*Dr Colman*) Tracy, who is thriving in the Edinburgh area, produced prodigious amounts of a protein called alpha-1-antitrypsin. We believe this protein will have considerable benefit in treating sufferers of cystic fibrosis. A production system has been developed using offspring of animals like Tracy and we are making something like half a kilogram of protein a week in Edinburgh and we are—

Mr Miller

82. This would be conventional offspring, are they?

(*Dr Colman*) They are created by normal breeding purposes, yes. There are about 300 of them at the present time. Their product is purified in a dedicated production plant in the Edinburgh area and that material is going into humans at this time. It is in clinical trials in this country. That puts in perspective, if you like, what we are doing.

Mr Batiste

83. As far as the new developments are concerned, you have already got to the point where you are able to produce a treatment for cystic fibrosis. What other areas do you think these developments could take you into?

(*Dr Colman*) In the medical areas?

84. Yes.

(*Dr Colman*) We have a flock of sheep that are making fibrinogen, which is another major human plasma protein which is known will work as tissue glue. So when you perform surgery on people you can actually apply this material to the open wounds and it is like an epoxy resin, you can just put it on and it seals the internal wound. You can then sew people back up and you do not get adhesions and because it is a biological glue it is taken care of, it does not remain in—

85. What other genetic diseases do you anticipate you may be able to provide assistance for?

(*Dr Colman*) At the moment we are working on two blood clotting factors, factor 7 and factor 9. Factor 9 deficiency is responsible for one of the haemophilia worldwide, haemophilia B. Many of these proteins we are providing presently are only available from human plasma supplies and in some cases there is not enough human plasma to supply anticipated needs. This offers, hopefully, a large scale, low cost production system.

Chairman

86. Could I just establish the arrangement by which you are developing these. Are these licences you have applied for to create a product of this kind and, if so, to whom?

(*Dr Colman*) Yes. When you start commercially developing any product there are all sorts of intellectual property out there which you need to negotiate. There is usually someone else. I think it is very rare for any company to develop all the intellectual property, have all the patents, everything in-house, so you have to negotiate licences with companies or academic groups, or research institutes, around the world. Sometimes you have to pay money up front, e.g. licence fees, but you usually also have to pay royalties on sales of the products. So it is quite a complex issue but typical in many sorts of business.

Mr Batiste

87. I wonder if I could also ask if Dr Wilmut has anything he would like to add to that list of potential benefits from the human medical point of view?

(*Dr Wilmut*) Not in terms of new products. In terms of diseases which can be studied as, for example, in the case of cystic fibrosis, it was suggested to us by people who are studying this disease that the sheep would make a good model for the development of either new drugs or perhaps gene therapy and so we are in discussions already with people.

88. Across what range of illnesses would this be used? Pretty well anything?

(*Dr Wilmut*) I think it would be limited to diseases in which the sheep was a better model than, for example, the mouse and I am afraid I cannot make that judgment.

(*Professor Bulfield*) In agriculture it is really in animal breeding. The UK leads the world in the animal breeding industry. It has the world's leading animal breeding industry, particularly in pigs. The situation we have at the moment is that we really need to develop this technology to use it in cattle and pigs, which would be the two species in which it would most be used. It probably is going to take us the best part of five years to do that. There may be quite a series of problems with pigs, but we expect it will be easier to transfer the technology to cattle, although it will be expensive. People have been using AI for the last 30 or 40 years. This type of technology is very parallel to it. You would keep your elite herds, which would be the top 10-15 per cent, and then you would use clones to bring the bottom part of the population right up to underneath the elite herds. So you would increase the average ability of, for example, a dairy cow by cloning the bulk of the population. You would have to be careful about inbreeding and transmitting genetic disease through the population, but one has to be careful of that with AI anyway and so the mathematical techniques to do that are actually already in place. So we foresee that it is going to have a big impact. We had an industry day at the Roslin Institute on 27th February to discuss this technology with the industry and they were extremely enthusiastic about it and the comment that I heard made was that this is going to have a bigger impact on the cattle breeding industry than AI did. So it is potentially very important.

Dr Williams

89. I find that prospect quite disturbing, the fact that in a sense you pick a "super" animal, whether it is highly producing or good beef producing, and then in a sense you are narrowing genetic diversity. This is one of the fears that the general public have of this field of research, the fact that you are seriously wanting to produce cloned animals for our consumption.

(*Professor Bulfield*) We have been doing that ever since we started breeding domestic animals which has been the last 4,000 years.

90. But this is much more dramatic.

(*Professor Bulfield*) I am not sure because the introduction of AI widened the genetic base of the population, it did not narrow it because all breeding was done with one bull and half a dozen cows on a farm. The advantage of AI (and this technology is parallel to that in some senses) is it enables you to bring genetic information or genetic resources from all over the world and introduce them into your population. The mathematics of diversity are very well understood. In our Institute we have the largest group of quantitative (mathematical) geneticists in Europe and this technology can be very easily incorporated into breeding plans in the industry. I foresee there being no problem at all.

Mrs Campbell

91. You talk about the mathematics of diversity. One of the problems in the plant breeding area is that what is widely grown by farmers is a very narrow number of varieties now in practice and in effect this means that those plant varieties succumb to disease and in fact have to be replaced at frequent intervals. We cannot keep on growing the same varieties for more than about ten or 11 years because then they succumb to disease and they are no longer so productive. In these circumstances, could you see that a limited number of animals with limited diversity genetically might produce the same problems?

(*Professor Bulfield*) I think the genetical advantages to be gained from introducing this technology, particularly into dairy cattle breeding, are enormous and make a huge difference to the average productivity of the herd. One would have to be careful one did not introduce a geno type widespread throughout the herd that had a problem. This occurs again with AI. A genetic disease was introduced into the Holstein-Friesian population by AI, so one would have to be careful about it. Again, this technology can be used to protect genetic diversity. There are 600 breeds of pigs in China. There are 800 breeds of cattle worldwide. The vast majority of those breeds are under threat because they are in very small numbers. A lot of these reproductive technologies can be used to preserve that genetic diversity. By using technologies like this and embryo freezing it is possible to retain that genetic diversity in vitro in the laboratory.

[**Mrs Campbell** *Cont*]

92. Can I just ask another question about aging because I think it was Dr Wilmut who raised the interesting question of how old is Dolly, is she 6 or $6\frac{1}{2}$, and I wonder what sort of implications you feel that will have, whether they are medical implications or animal breeding implications. Are you saying that we can study the process of aging more effectively and perhaps find ways of halting it?

(*Dr Wilmut*) I think there are both implications. Clearly if the process of nuclear transfer does not reset the clock it would have implications for any use of the technique, but understanding what has happened to those cells when we have used them will teach us a little bit about the natural process of aging.

Dr Bray

93. Is AI necessarily going to prove a realistic model for cloning because there is a drastic stage of fertilisation of the embryo in AI?

(*Professor Bulfield*) It is not a perfect model, but it is a model in the sense that it is providing one side of a geno type and by its effect it is distributing genetic information widely and it also has the same potential for causing inbreeding problems or for causing narrowing of the genetic base. So it is that genetical side of it that is similar. It is not quite the same, but it presents a whole series of issues which are very similar and the mathematics to deal with those issues have been developed. I do not think it is very widely understood that to maintain genetic diversity in a population of animals you need around 100 animals. It is not a very large number when you consider that we have got several million dairy cattle. You can maintain almost perfect genetic diversity with that.

94. Statements like that can be made. Indeed the AI model is made because of the vast numbers of animals which are now produced by AI and you have a very large population to observe. Is it not going to take some time to be equally confident that its diversity arguments do apply without the stage of selection that there is in embryo fertilisation?

(*Professor Bulfield*) We will always retain selection. As I said in my introduction to this area, we will keep ten or 15 per cent as an elite herd. We will continue to carry on selection. We will continue to carry on and improve the population. It is in disseminating that improvement through the main national herd that you could foresee a situation where the elite herd would be in the hands of the breeding companies or the breeding organisations, of co-operatives or whatever, but the general use of that elite herd would be disseminated straightaway throughout the whole population thus bringing the whole population right up to the level below the elite herd.

(*Dr Wilmut*) We should not be too anxious about the speed with which this might come about. I know you should never predict, it is folly, but it will surely be a long time before this technique has got the success rate and the sufficiently low price needed to be applied on a very large scale. The success rate of 1 in 29 for Alan's use for the pharmaceutical industry for research is acceptable but for commercial breeding it is simply not acceptable.

Chairman

95. Can we just have, for the record, the sort of timescale you are talking about before the results which Professor Bulfield was describing would actually occur?

(*Dr Wilmut*) I do not think we are contradicting ourselves. To make it work at all in the other species it would require a small number of years work, but for a farmer to wish to use this on a large scale, as it has been envisaged here, to produce most of his herd of dairy cows the success would have to be much higher than it is at present and I think you should not expect that in less than ten or 20 years.

(*Professor Bulfield*) Chairman, this is one of the problems we have, this technology has only been done once. We now have the technical problem of improving its efficiency, adapting it to other species, particularly the dairy cow, and that is quite a lot of basic scientific work that it might be required to do. We do not know what problems we might find in other species. That is what I said at the beginning, it may take five or ten years to get it and then we have to work out how we can incorporate it into breeding schemes. We are not looking at something that is going to happen very quickly.

Sir Gerard Vaughan

96. I understand your comments about the size of herds and things like this. Would your interest also go to smaller groups of animals, for example more specialised groups like horses?

(*Professor Bulfield*) Again, we do not know if there are problems in adapting the technology from one species to another, but there is the possibility of proliferating a geno type wherever you might want to do that. In the last few days we have had discussions with a Food and Agricultural Organisation of the United Nations who have a major problem of small populations of domesticated animals and breeds which they want to maintain. At the moment they are looking at embryo freezing or semen freezing and they thought this technology might be useful because in many ways collecting material from the field is quite difficult. To collect small samples of cells from a bit of fur pulled out of the back of an animal is a lot easier than bringing them to a laboratory and collecting embryos. We do not know ourselves yet what the issues might be about going down that road, but it is yet another intriguing possibility for the future.

Dr Williams

97. I accept your reservation that this technique's application is not going to be in a year or five years but it could be there in 20 or 30 years time. It seems to me that the scenario that you are painting is one where you have a small number of elite herds to maintain your genetic diversity but then in 20 or 30 years time your large flocks of cattle and sheep would be ones from cloned animals because of their high productivity. Is that not in vagrant disregard of the Biodiversity Treaty we signed at Rio just a few years ago?

[**Dr Williams** *Cont*]

(*Professor Bulfield*) There are two issues about biodiversity. One is about biodiversity in terms of maintaining the biodiversity of species and then maintaining within a species—and most of the treaty involves species diversity—the genetic diversity. Most of our breeds of animals and plants were produced in the 17th and 18th century and they were mostly fixed on what the animals looked like. In fact if you look at the genetic difference between a lot of these breeds, they are almost non-existent. The genes that occur in one, with the exception of the coat-colour genes, will occur in another. The genetic differences between them are illusory. The biggest change that has happened is not really the technology of AI but the fact that then led to a consolidation of breeding in the hands of smaller numbers of breeders, whether these are co-operatives or companies, and that organisation of the structure of the industry made almost a bigger improvement than the introduction of the technology, but the technology permitted that restructuring.

98. Is there not something a bit nonsensical here in that the motive for this is economic performance, cheaper animals, cheaper meat and so on when our problems in Europe are ones of over-production and the big food mountains that we have had over the decades? We do not really need these technologies in agriculture.

(*Professor Bulfield*) I am afraid it is not so straightforward as that because we have a problem of efficiency. If we do not keep our agricultural industry working at top efficiency then we are just going to give over our markets to the Netherlands, for example, where their agriculture is incredibly well organised. Although we have an over-production issue in Europe but not in the rest of the world, that does not mean to say that we can forget about the efficiency of production. We have to retain efficiency. If it is going to cost us more to produce our dairy cattle and to produce milk than it is going to cost the Dutch then we will be giving over our markets to them and in this technology we have an absolute world lead.

Dr Williams: But if there was agreement across the European Community that certain techniques could not be used, like cloning of animals for food production, then that is not the problem.

Dr Jones

99. Those are exactly the arguments used for the arms trade, are they not, if we do not do it somebody else will?

(*Professor Bulfield*) That was not the argument I was making. The argument I was making was that if we can produce our milk at 15 per cent cheaper because production has been improved by improving efficiency of breeding stock then that is going to improve the competivity of our industry. That is the point I am making. Scientific breakthroughs are going to have to be incorporated into agriculture all the time even though we have got over-production. Even in an over-producing community we are still in competition.

Chairman: Let us bring PPL into this.

Mr Miller

100. In the context of this very long-term research, what is the relationship between Roslin and PPL? Do they sit side by side? What is the commercial relationship? What is the scientific relationship?

(*Dr Colman*) As you might know, PPL was really founded out of technology developed 10/12 years ago in the Roslin Institute and this is the technology which has led to Tracy, many of her lookalikes, and other animals producing valuable products. The relationship has always been quite a cosy one but not a monopoly[1] in the sense that we have funded work in the Institute for a number of years since 1987 and also we have an agreement with the Roslin Institute to pay them royalties on any products or sales we make of material which exploits their inventions. That is the type of relationship we have had to date and one would hope that is the type of relationship that will continue into the future.

101. What scale is that at the moment?

(*Dr Colman*) In what sense?

102. In terms of the amount of royalties.

(*Dr Colman*) I think we have only recently in the last year paid any royalties at all because one of the points people do not often realise is most bio-technology industries are loss makers for many years and we do not expect to put our first bio-medical product on the market until 2001. It is from 2001 onwards, if successful, when we believe a good royalty stream will flow to Roslin. In the meantime if we sell services of certain sorts to other companies then modest royalties are and have been paid to the Institute.

103. Against the background of the public concern that has just been expressed about some of the issues and recent press reports, you must have been able to convince your financial backers, your bankers, that there is something very positive there that is going to be beneficial to health service markets on a big scale here, otherwise they would not have stuck with you?

(*Dr Colman*) That is right.

104. That is one of the interesting things about the model of financial support for small companies. Presumably they have given a commitment to stick with you for some years ahead because of the timescales that Professor Bulfield has been talking about?

(*Dr Colman*) For ten years we were a privately sponsored company, mostly funded by venture capital and they were giving tranches of funding every two years, so we always needed more funding before the next lot of sheep had been born because the generation time of the sheep was greater than the generation time of venture capitalists.[2] It was a struggle sometimes getting the money but, as you would know, we launched on the London Stock Exchange last June and attracted quite a large treasure trove. We only expect that to last two to three years, three years I think we said, depending on success, and we might have to come back to the

[1] *Footnote by witness:* I actually meant "not a one-side relationship with all the benefits flowing to PPL."

[2] *Footnote by witness:* I meant "the generation time of venture capitalist's *patience*."

[**Mr Miller** *Cont*]
market before we make profits. It is a long haul. We are not making great riches at the moment. We do not expect to make profits until the next century.

Chairman

105. When you started Treasury rules would not allow public bodies to hold equity stakes in spin-off companies. I assume you had no private capital at that point. What is the position now?

(*Professor Bulfield*) When the company was established it was before either myself or Dr Colman were involved in either the Institute or the company. Scientists at that point tried to attract the interest of the major United Kingdom pharmaceutical companies. It was only when that failed that PPL Therapeutics was established. To a large extent it was mothered by the old Scottish Development Agency. They made the contacts and put everything else together. They are now Scottish Enterprise and they are a shareholder in it. In those days, it was before my time, I understand that the Treasury rules meant that the Institute could not have equity in the company and neither the Institute nor BBSRC has equity in the company. Latterly, some of the scientists involved have become consultants for the company and some scientists do have personal equity in the company, although not Dr Wilmut. I might add that the Institute does not particularly favour PPL Therapeutics even though it gave birth to it. This technology we have developed through Dr Wilmut's work has three patents associated with it. We have licensed them to patent to PPL Therapeutics for their area of interest only. For example, for animal breeding we have not licenced the patents.

106. PPL do not in fact enjoy the intellectual property rights of all the things they undertake?

(*Professor Bulfield*) Not in the particular patents. In Dr Wilmut's case we only license those patents for their area of interest.

107. Could we just have a comment on the shareholding of Roslin.

(*Professor Bulfield*) Roslin or PPL?

108. I beg your pardon, PPL. You mentioned Scottish Enterprise were the original stakeholder. Who are the main shareholders?

(*Dr Colman*) You will be aware that when you are transformed from a private company to a public company you lose track of who the investors are, at any one moment in time, because it is public. The major investor in our company still remains one of the original venture capitalist investors which is Alan Patricof & Partners based here and in the US and in France, but we do have companies which hold equity stakes in us—Novo Nordisk is a major shareholder—but the majority of shares are held by a variety of pension and institution funds nowadays.

Dr Bray

109. Do Scottish Enterprise retain a shareholding?

(*Dr Colman*) I believe that is the case but I am not absolutely sure because again there has been a lot of trading in the last week and I do not know who the current shareholders are. I can find that out for you but I do not know at the moment.

Chairman: Drop us a note on that.

Mr Batiste

110. Is it policy for Roslin to maintain for itself patents in all its activities that are patentable and that you will incur yourselves the expense of protecting it worldwide if that proves necessary?

(*Professor Bulfield*) No, our policy has changed over the years. The very first patents we had on Tracy, which was the original transgenic work, were actually assigned to PPL Therapeutics. Those were the first patents we ever took out. Our policy is now if we identify a bit of intellectual property that we require to patent, we file the first filing of the patent. In between the first filing and our requirement to extend this to European states we try to look for a commercial partner to help us exploit it, mainly because we are not in a position to do that and if we get into difficulties with a patent, and in one case we had to spend a whole or half day in the European Patent Court, that becomes very expensive and we cannot afford to do that. We try initially to find a partner in the United Kingdom. In almost every case, I would hesitate to say every case, of the 17 patents we have filed and one licensed it has been to a United Kingdom company. We do not licence them solely to one, it depends on the field of use. As I explained earlier, there would be no point in licensing the patent in Dr Wilmut's work to PPL for animal breeding because that is not part of their business.

Chairman

111. On this question of shareholding at PPL, do you have executive share option schemes and do the staff participate in Roslin as well?

(*Dr Colman*) At PPL everyone who has been at the company for more than six months has share options.

112. The staff at Roslin?

(*Professor Bulfield*) Staff at Roslin are permitted to have shares in PPL. In fact neither Dr Wilmut nor myself have them but I believe one or two of my colleagues do.

Dr Bray

113. Are there shares options, not just shares, being offered to staff at Roslin?

(*Professor Bulfield*) I imagine they are options as well as shares but I would have to find out the details from the individuals involved.

Chairman

114. It is clearly not a significant management practice as it were?

(*Professor Bulfield*) No.

Mr Miller

115. Just to clarify that relationship a bit further. Are any members of the board of PPL current or recent employees of Roslin?

(*Dr Colman*) The board? The management board? No.

116. Directors of the company?

(*Dr Colman*) No, none of the directors are from Roslin Institute at all.

Sir Gerard Vaughan

117. You will correct me if I am wrong but looking at the BBSRC accounts it appears that PPL took over three of the research institutes or the staff of them and some 17—I can see you are going to correct me—patents and a total funding of something like £23 million.

(*Professor Bulfield*) Well, I think there must be a misreading there. There have been so many changes from the ARC to AFRC to the BBSRC. What has happened to the Roslin Institute is that it was a wholly-owned creature of the old AFRC and BBSRC. In 1995 it was established as a company limited by guarantee and a Scottish charity. The company, of which I am Chief Executive but also Director of the Institute, only owns two things, a 12-year lease on the land and buildings and the existing patents, otherwise all the employees are still BBSRC employees. There has been no wholesale transfer of funds from the BBSRC to PPL. Our relationship with PPL is exactly the same as our relationship with any other commercial company. If we found we were getting a better deal somewhere else I am afraid we would go somewhere else.

118. Does that mean there has been a transfer of staff?

(*Professor Bulfield*) No, I do not think there are any significant employees.

(*Dr Colman*) Can I make a point here. When this company started in 1987 it was very difficult to attract staff to leave Roslin to join the company because the type of company we were was looked on as so uncertain and fragile that despite the fact that government institutes are not immune from redundancy we found it very very difficult to recruit from Roslin employees. I was an academic in Birmingham at the time and the first scientist recruited to PPL actually worked in leased laboratories down in Birmingham for about a year before we could move up into the Edinburgh area. It was very difficult to get anyone from anywhere at that time.

(*Professor Bulfield*) There are no senior members of Roslin staff who have ever moved to PPL. There may be the odd technician who has moved from time to time but no-one with any control over intellectual property rights or senior scientists.

Dr Jones

119. Could you tell us what are the three patents you have in connection with this work?

(*Professor Bulfield*) Yes. There is one patent which is on how we handle the recipient cells, how we handle them in such a way that we were able to transfer the nuclei from them. The second patent is on how we treat the recipient cell and the third patent is on the original cell line we used in the experiment a year ago involving Megan and Morag. We thought at the time that cell line was important. We now know it can be done with other cells. There are two important patents; condition of donor cell and the condition of the recipient.

120. You said the handling of the recipient cell and how you treat the donor cell.

(*Professor Bulfield*) And the original cell line. We do not think the original cell line was unique. We thought at that time it was unique.

Chairman

121. Can I ask which was the difficult patent that involved you in costly arguments with the European Patent Court.

(*Professor Bulfield*) We have not got to that stage yet. I know it has been said in the press that we were holding up publication until we filed patent but in actual fact we filed patents on 31 August 1995 before the first paper. At the moment those have not got to the European Patent Office.

Dr Jones

122. When did all this work start and at the start how was it regulated? What sort of hoops did you have to jump through before you got the go ahead?

(*Professor Bulfield*) I will talk about the regulations and then if you want to know about the technical details. In our memorandum we indicate that there are no specific regulations governing this area at all. That is a point we might wish to talk about because in fact the Ministry of Agriculture's Banner Committee has something to say on that area. I will come back to that in a minute. Our work in this area is governed by two sets of regulations, one is the Animal (Scientific Procedures) Act 1986 which all research laboratories working on animals have to accommodate and deal with, and the second one is the Advisory Committee on Genetic Modification Regulations. They do not specifically apply to the experiments we have done so far because we have done no genetic modifications of cells but we are planning to do so. In addition, the Institute has its own animal welfare and experiments committee which considers the ethics of experiments not from the human point of view but from the point of view of the ethics of doing experimentation on animals. That includes lay members of the Institute and as an automatic member, the local Home Office inspector.

123. Essentially you went through the normal procedures for any scientific experiment that goes on in institutes all over the country and presumably project approval through the BBSRC as well.

(*Professor Bulfield*) The core funding for this project came from the Ministry of Agriculture, 65 per cent, although there is some BBSRC funding as well. We fill in application forms for extending work in three year tranches from the Ministry of Agriculture on a standard form which gives milestones and objectives. If I could just mention about the Banner Committee. I think this is fairly important. I do not

[Dr Jones *Cont*]
think many people realise that when Mr Gummer was Minister of Agriculture in 1993 he established a committee of which I have the report with me: "Report of the Committee to consider the Ethical Implications of Emerging Technologies in the Breeding of Farm Animals". This committee was under the chairmanship of the Reverend Professor Michael Banner and I was the only scientist member of that Committee and it reported in 1995. It had 17 recommendations of which number two was that some sort of standing advisory committee should be established to keep an eye on ethical issues arising out of the new technology. Cloning was discussed in this committee report on pages 35 and 36 and even the potential impact of cloning on biodiversity was discussed in chapter 7, although cloning at that time had not been achieved. Recommendation two recommending that there should be an advisory committee along the lines of the other committees we have in similar areas was the only recommendation the Government rejected.

124. As you know, this Committee had a major inquiry into human genetics and Dr Colman mentioned that we did come up to Edinburgh. I remember very well the presentation you gave us on Tracy. I do not remember any mention being made of this kind of work. I would have thought it would have been even more relevant to our inquiry at that time than the transgenic work with Tracy. I do not remember it being mentioned. Why was it not mentioned? It must have been in the pipeline at the time.

(*Professor Bulfield*) Can I make some general comments about how science evolved. Science is not evolving by leaps but a general incremental steps over the world. Even within this project, the research started some eight to ten years ago, as Dr Wilmut suggested, trying to basically understand how we could grow cells in culture, genetically modify them in culture and then transfer them into animals. At that time, this was a year ago—

125. No, it was about two years, two and a half.

(*Professor Bulfield*) At that time we had not even completed the experiments on Megan and Morag. We certainly had not published work at that point on transferring nuclei from embryos let alone transferring nuclei from differentiated cells. In case it is being alleged that we hid this information on Dolly for a considerable period of time, Dolly was only born seven months ago. In the three or four months after that we had to do a lot of DNA fingerprinting on her to make sure she was a clone. If we had published it before we were certain about that we would have made considerable fools of ourselves if we had got it wrong. We then had to go through a three to four month reviewing process for journals. The rules of scientific publication are that you must not put into the general public domain any paper that is going to be published in a scientific journal otherwise they will not accept it. We got this research into the press and into the public debate as soon as we possibly can. As you can imagine, this scientist does not want to sit on something which is probably the biggest scientific advance of his career, he wants to tell his colleagues. I believe seven months is a very short period of time. A scientific paper can be held up by a journal for a year. I do not think we have in any way hidden or not put this information into the public domain. The first paper in *Nature* on the embryo nuclear transfer was published last year and that paper alluded to the work going on in Roslin at that particular time.

126. You are referring there to the Banner Committee report published in 1995 raising it as an issue? I cannot understand why it was not raised with us when we came to Edinburgh just as something being looked at as an issue. Obviously our inquiry was about human genetics not about transgenic sheep.

(*Professor Bulfield*) Two years ago we had not got to this point. A year ago when we published the work on the nuclear transfer of embryos there was considerable media interest and, as I say, the issue of cloning did occur then but, quite frankly, only when the sheep was on the ground and people can see it does the impact of it really come into it.

127. This really raises an issue about whether you can actually prepare the public for discoveries of this nature. As you say, the whole issue was to some extent in the public arena but nobody picked it up until Dolly was on the ground.

(*Dr Colman*) Could I respond to the question of why this was not mentioned two and a half years ago. I have to say John Gurdon was mentioned as a true pioneer of nuclear transfer methods in his pioneering work in the early 1960s and 1970s in the UK. I actually did my PhD with the now Sir John Gurdon so I was well aware of what nuclear transfer had achieved. If anything, that made me more sceptical about the chances of the work that was going on in Roslin actually succeeding. My experience with nuclear transfer methods 20 years ago made me feel it was almost impossible. There was no point for me now in commerce to raise expectations of potential investors by saying there is this wonderful technology around the corner, because my credibility would have been damaged and I did not think at that time, two and a half years ago, that this was a feasible technology.

Dr Bray

128. Can Dr Wilmut confirm that he came to a meeting arranged by Lord Winston in the House of Lords a few months ago.

(*Dr Wilmut*) Absolutely, November 5 I think it was because there were fireworks outside. May I just add a little bit of detail just to confirm the impression that has been given. The first time that we had real optimism about the technique would have been at the birth of the group of lambs of whom Megan and Morag were survivors. That was approximately one and a half years ago, July and August of 1995. Until then there was a higher than normal loss of foetuses during pregnancy so until there were lambs alive we could not be confident the technique would work. We would not have had anything to bring you until that summer.

Dr Williams

129. To understand, there is no regulation whatever that prevents research in cloning or even its application in agriculture?

(*Professor Bulfield*) In farm animals there is no regulation other than the Home Office regulations which actually indicate that we cannot release an animal from the Animal (Scientific Procedures) Act until an inspector approves it. If there were something wrong with those animals in terms of animal welfare then certainly the inspector would not release it from the Act, if there was an ethical issue I am not sure what attitude the inspector would take. They do not tend to comment on the ethical issues, it is more on the animal welfare issues.

Chairman

130. Can I ask for the record that kind of inspection, ie the protection of the animal kind of inspection, is that undertaken with some regularity?

(*Professor Bulfield*) Yes. We do not know when the inspector is going to arrive.

131. They do a proper job?

(*Professor Bulfield*) Absolutely, yes, there is no doubt about that.

Dr Williams

132. Your 1995 Banner Committee did make a clear recommendation that there should be an advisory committee something like the one set up for human genetics.

(*Professor Bulfield*) The model we were thinking about at that time was the Advisory Committee on Genetic Modification because that was the model we had. Some of us in 1982, when genetic modification had first been achieved with animals and was being started with farm animals, suggested to the ACGM that they looked into this area and in fact a transgenic animal working party was established which had not only HSE representation but Home Office, MAFF and DoE representation on it. It formulated what has now become known as ACGM note number 9 which is governing genetic modification with transgenic animals of all sorts right from Drosophila through to mice to farm animals.

133. That particular committee, is it mainly scientists and exclusively scientists or some lay people?

(*Professor Bulfield*) The Advisory Committee on Genetic Modification, I was a member of it for eight years. It has a nominee of the unions on it because the health of workers is involved with the HSE and it has quite a wide range of members.

Chairman: We will obtain a list for the Committee.

Mr Batiste

134. Just coming back for a moment if I may to publication and judgments you have to make on publication, clearly if there is going to be something patentable you will want to ensure that you do not prejudice your ability to patent by prior publication. I understand you have got these three patents in place already but presumably there is now the potentiality of a tranche more patents to flow from it. How does that interact with the timescales?

(*Professor Bulfield*) Our record for patenting is five working days because we had somebody wanting to go to a conference. This was a patent we had on producing transgenic chickens. Somebody wanted to go to a meeting and we realised that we had not patented it and we did it in five days. That indicates to you while you are preparing all the material for publication and getting it in that format you are really preparing a patent although a patent is considerably more detailed than a publication. Therefore the two processes are interconnected. Perhaps Ian would like to make a comment on his patents and whether he felt they impeded his publication or created any other problems.

(*Dr Wilmut*) I think there would have been a small initial delay because of the need to prepare those patents but it really is a considerable labour to produce, particularly for *Nature*, the very short precise publications that they require at the level of accuracy that is appropriate for a journal like that. To publish in six or seven months is almost as quick as it is possible to obtain it.

135. You do not feel that there was any noticeable delay in your ability to talk to your colleagues about your progress as a consequence of the need to develop patent applications alongside it?

(*Dr Wilmut*) I think it is important to mention one other thing. *Nature* is unique is imposing a rule that you must not mention things in the public domain. If it had gone to any other scientific journal as far as I know we would have been able to discuss it more freely. It is a trademark of *Nature*.

(*Dr Colman*) Patent issues can be quite complex. In this particular instance there was no delay to publication due to patent considerations. There can be delays and recent rulings of the Technical Board of Appeal of the European Patent Office are actually making it more difficult for academic groups to publish in a timely matter. Even if you file and then you publish, you can compromise further additions to those patents. It is quite a complex issue but it did not impede the publication of this particular paper whatsoever.

Chairman: I am sure the European Patent Office has never done anything in five days!

Sir Gerard Vaughan

136. May we take it as things are today you see the regulatory system as reasonably satisfactory and efficient or would you want to see changes?

(*Professor Bulfield*) I was a member of the Banner Committee and we did raise this concern about whether there was a framework for wider public discussion of ethical issues in animal breeding. We did realise that cloning was coming along because I was there and I knew we were working in that area. I think it is more that there is public concern than that there are any substantive issues. I do not actually feel myself there are likely to be some substantive issues. I do not feel this technology we are talking about today is that much different from artificial insemination but there are other people who do and the important thing is to make sure that the public

[**Sir Gerard Vaughan** *Cont*]
believe there has been a proper discussion of the ethical issues. I am not sure from the various reports in the press and on television and so on that this has actually happened in this case. There are clearly some concerns not just from the human application of it but its use in animal breeding.

137. Would the regulations still apply if the experiment had been halted at the proof of concept stage, you knew that it would be effective and you had stopped then?
(*Dr Wilmut*) Until you have a live lamb you have no proof of concept and therefore you would require the full set of regulations that are in place at present.

Dr Bray

138. Would they have applied if the embryos were cultured and formed outside a living recipient?
(*Dr Wilmut*) If everything was obtained from slaughter house material then it might not have required regulation. It is at a particular stage in gestation when it begins to come under the Act or of course, as we do in our experiments, if you obtain the unfertilized eggs from donor users.

Mrs Campbell

139. Professor Bulfield, there is a tremendous interest obviously in using this particular technique on species. We are interested in exploring the scientific possibility there. Is it true that it is easier to clone sheep by this method than any other species? For example, how significant is the delay before the genome is transcripted?
(*Dr Wilmut*) It is true that the transcription is rather later in sheep and cattle than in the human which is one stage earlier and the mouse is one earlier still, the two cell stage. In general terms it does seem there is a correlation with other techniques of nuclear transfer, that the later transcription is initiated the more effective is nuclear transfer. We do not have enough information to know the impact of this on the success of our new technique yet. My own personal estimate would be that the new technique will improve things in species like the pig, which is a similar type to the human, but it might be that the efficiency is even lower.

140. How does the transcription time of humans and pigs compare with the transcription time of sheep?
(*Dr Wilmut*) The pigs and humans are approximately at the four cell stage, the sheep and the cows are at the eight cell stage.

141. I am not clear whether it took two or three sheep to make Dolly. As I understand it there was the sheep which gave the egg, there was the sheep which gave the mammary cell and the sheep within which Dolly was grown to maturity. Would it be possible to use the same technique with a single sheep?
(*Dr Wilmut*) I think there may be one more sheep for the sake of completeness.

142. Four sheep.
(*Dr Wilmut*) The present culture systems in the laboratory are inadequate so with the majority of the embryos they are grown in a temporary recipient sheep. It is our intention, our objective, to bypass the need for this as quickly as we can. So if you were to consult the original paper you would see that some were grown in the lab and some in the temporary recipient. I think all of the eggs in the group I have described were grown in a temporary recipient. I am sorry, I have forgotten your question.

143. My question was it took two, three or four sheep to create Dolly, could you do it with just a single sheep?
(*Dr Wilmut*) No, in practice.
(*Dr Colman*) As Ian has said, if you can get round this problem of the culture of using a temporary recipient then, yes, in principle you could take the mammary gland cell of a sheep, freeze it down if necessary and transfer it to the ovulated egg from that sheep at a later stage and put it back into that sheep. You would need that culture stage to have been sorted out.

144. So theoretically you could do it but practically at the moment you cannot?
(*Dr Wilmut*) The question would be why you would want to do it. This procedure would certainly be covered by the Animal (Scientific Procedures) Act and you would not be allowed to do that number of procedures on an animal without an exceptional reason, which I cannot imagine and therefore that is why I said no.

Dr Jones

145. But having the recipient egg from the donor nucleus from one animal is the only way in which you could have a genuine clone, is it not, because of the mitochondrial DNA? Is there any interesting work that could arise from this in actually finding out what mitochondrial DNA does? Dolly is not a genuine clone because she has got DNA from two sources.
(*Dr Wilmut*) You are absolutely right, of course. We used the shorthand of describing them as being genetically identical to cover the qualifications that you have introduced, the cytoplast and the mitochondria and also uterine effects and other sources.

Mr Miller

146. Just to follow that up so that we understand and the public outside: if it is not a genuine clone, how different is it in practice?
(*Professor Bulfield*) In the mitochondria there are around 20 genes, in the nuclear genome there are around 70,000. There is not much genetic variation using the mitochondrial genome so it will be a small percentage. In fact, you will notice in the paper that Dr Wilmut does not use the word "clone", he is very careful in his choice of language. I do not think that would become an issue in the scientific community. It is true, it is 99.9 per cent a clone or something like that and but for all the nuclear genome it is genetically identical.

147. And the variance from the 100 per cent is an irrelevance in terms of the—
(*Professor Bulfield*) We do not know if it is a total irrelevance. This is another interesting experiment to do, to look at the contribution of the mitochondrial

[**Mr Miller** *Cont*]
genome in some particular cases. There are inherited diseases that are due to a deficiency in the genes of the mitochondrial genome.

Dr Jones

148. You could have two kinds, those that are from one animal and those that are from two animals with different mitochondrial DNA and that might lead you to interesting lines of research.

(*Dr Wilmut*) That is absolutely the way you would address your question, yes. Instead of trying to do it within the same animal you would take a number of embryos either from a female or ideally if you are working with an inbred animal like the mouse then you produce them from a line and transfer a common group of nuclei into a variety of different mitochondrial backgrounds. That is how you would address the question you are asking.

Dr Bray

149. Dr Wilmut, if regulation did not prevent it how easy might it be scientifically for someone somewhere to apply your method to the cloning of humans?

(*Dr Wilmut*) It would be my belief that if you really wanted to do it it could be done. I have hesitated already to make predictions and I hesitate to do it again but I am sure if you really wanted to do it you could do it.

150. Over what kind of time period of development?

(*Dr Wilmut*) I think this is really almost a distressing conversation if you were to look at the table and see how many unfertilised eggs we worked with, which must be of the order of a thousand, and ask the question where you would get these from in your hypothetical experiment. If you were prepared and able to make that sort of effort then you might expect to make significant progress in one or two years.

151. A conclusion from that is that the widespread concern about the cloning of humans really does require international regulation at a fairly early stage?

(*Dr Wilmut*) Yes.

(*Professor Bulfield*) Yes.

(*Dr Wilmut*) Yes, absolutely. I have said quite a large number of times in the last week that it is the unanimous view of the group within the Institute and in the Company that we would find this sort of work with human embryos offensive. We can see no clinical reason why you would wish to make a copy of a person. We are pleased that it is already illegal in this country. We would support wholeheartedly the idea of prohibition in as effective a way as possible.

(*Professor Bulfield*) I was just going to add that if we cannot go forward by prediction at least we can look backward and see what has happened in the past. As I mentioned earlier, genetic modification was achieved in mice in 1982 and in farm animals in 1985. To my knowledge in those 15 or so years there have been no attempts to apply genetic modification directly to humans, to the germ line of humans, although there has been an attempt to use it in gene therapy. Therefore, I think this technology will fall into that category. I can see that there could be *in extremis* some circumstances in which somebody might apply it somewhere in the world but generally speaking I think the need to apply it does not exist. It may be in the future something might happen that would demonstrate this technology might be useful but we cannot see it at the moment.

Chairman

152. We heard yesterday about the legal structures which apply to the cloning of human cells by this method. Much depends on the definition of the word "embryo" and that of course is in the existing legislation. The points put us to were: "A live human embryo where fertilisation is completed, and references to an embryo include an egg in the process of fertilisation, and, for this purpose, fertilisation is not complete until the appearance of a two cell zygote". Would you agree with that?

(*Professor Bulfield*) Yes.

153. Do you consider the embryos you created had been fertilised?

(*Dr Wilmut*) According to that definition I think no.

154. Any comment, Professor Bulfield or Dr Colman?

(*Professor Bulfield*) No. I believe the wording in the Act is that it is something like "an embryo in the process of fertilisation". An embryo cannot be in the process of fertilisation because it is only an embryo after fertilisation.

Dr Jones

155. "An egg in the process of fertilisation".

(*Professor Bulfield*) In that case this is an egg. The oocyte is an egg but it has not been fertilised and it never is fertilised because the nucleus is transferred to it. It is a very nice point but I would have thought the intention of the Act is clear.

Dr Jones: The intention!

Chairman

156. A nice point it may be but it has to be a point at law which has a definition which is appropriate to the circumstances.

(*Professor Bulfield*) Yes, I agree.

Mr Miller

157. Professor Bulfield, you used the word you "think" it is clear. I do not think anyone around this room can be absolutely certain.

(*Professor Bulfield*) I am not a lawyer.

158. From the point of view of the scientific community what would be the best solution, to ban clearly and unequivocally the output of certain research, ie research that is designed to produce an identical human being, or to work on the definition of the embryo? What would your preferred route be?

[**Mr Miller** *Cont*]

(*Professor Bulfield*) While Dr Wilmut is thinking about that one if I could answer and say I understood—and I do not know, I am not a lawyer—we were in a belt and braces position here, that the Human Fertilisation and Embryology Authority had the right to license experimentation and therefore would decide in this case not to license it. Maybe given that technology is moving it is often more preferable, and this is how the Home Office works with the Animals (Scientific Procedures) Act, to ban experimentation as the inspector shall from time to time decide and therefore to leave it to the judgment of something like the Human Fertilisation and Embryology Authority. If you start covering up little holes in the legislation as the technology moves on we cannot predict if something else might come along that again might find a hole in it. I would have thought to give the powers of judgment to the Human Fertilisation and Embryology Authority might be the right way to go about it.

Chairman

159. Of course it was they who came to see us yesterday. There seems to be a view which supports the contention that it is a crucial thing that the word "embryo" be defined in law in such a way that science is clear as to what it actually means. There is no need to press you, Dr Wilmut.

(*Dr Wilmut*) I do not think I would offer a different view.

Sir Gerard Vaughan

160. Can I ask about outside this country now. The announcement that American scientists have cloned monkeys, that is not strictly comparable since they do not start from adult cells, but to you knowledge is any similar work to yours being done in other parts of the world?

(*Dr Wilmut*) If I may answer, Chairman. Certainly, yes, there are groups particularly in Australia and the United States who were already working with the process of nuclear transfer. In fact, it is fair to say that ten years ago we began by building upon research particularly from the United States and have simply, in a sense, been more fortunate. There were groups already active in Melbourne that I can think of and a number of universities in America using nuclear transfer. As the objective was to be able to introduce a precise genetic change there were other groups who were interested in trying to isolate embryonic stem cells or the related cells which can be derived from primordial germ cells in some laboratories in the United States and Australia. I can also think of people in Europe, in Italy and France. There is a lab comparable to ours funded by INRA which is just outside Paris. There will be quite a number of laboratories who are working in a similar way.

Mrs Campbell: In fact you scored a resounding first, Dr Wilmut. Is that because we have better scientists in this country or is it because our regulations are perhaps not quite as tight as they are elsewhere?

Chairman

161. Do not be modest!

(*Dr Wilmut*) I think why we have been successful is because of persistence and good fortune. You have to work in this area for ten years and to build in a systematic way. One of the things that has been a bit difficult in the last ten days is the way things have been personalised. The first person to realise the fact that we were going through a barrier was a colleague of mine, Keith Campbell. This sort of research does depend on having a multi-disciplinary team. I think it is those things of persistence and then good fortune in the end.

Mrs Campbell

162. Can I just ask a follow up question. You say you have been working on this for ten years and I think in that time you have been funded by BBSRC mainly to do this work.

(*Dr Wilmut*) It would be a mixture. We started originally with a different commercial collaborator in DTI funding and then unfortunately when that came to an untimely end MAFF started to support this area.

163. Is the security of that funding quite important in trying to use this kind of discipline?

(*Dr Wilmut*) Absolutely. It follows from my first answer that you do need to address this sort of problem for a long time. There would have been very few people who would have predicted that we would have got to this particular outcome when we started ten years ago.

Mr Batiste

164. Since *Jurassic Park* the public has had some understanding of what is involved in the technology, albeit relatively imperfect. The problem with this that is being faced, as you will have faced this week in the public debate about your discovery, is that all technologies have a good side and huge benefits that they can bring, which you have described today, and used in unethical ways can have very bad down sides, which is one of the reasons perhaps why this is going to be one of the most crucial technologies for the future of our species. The problem that you have described already about disclosure is that it seems to be almost impossible in the context of what you have described to be able to have any kind of public debate about the issues involved before the discoveries are made. Is that a fair judgment or is there some way in which we can anticipate a discovery, even if some projects may or may not come to anything and you do not want to look silly and have egg all over your face? Is there some way to anticipate where the science is going, the sorts of issues that are going to emerge over the next ten to 15 years so they can actually be debated upfront rather than after the event?

(*Dr Wilmut*) There are two factors which make this difficult. One is predicting the outcome of a particular project. We have already documented the fact that people did not expect us to reach this point. The other is that we are collectively notoriously bad at predicting the way in which a technique will be

[**Mr Batiste** *Cont*]
used. Even if you make the assumption that nuclear transfer will be successful people will perceive different uses for it over a period of time. There are two very substantial hurdles in trying to carry out an effective assessment before a project is begun.

165. If that is right it will be justified by the film makers who will speculate if the scientists do not.

(*Professor Bulfield*) In many ways we can have a general discussion about where science is going. Dr Wilmut is completely correct that in specifics it is very difficult to predict where they are coming from. In that way science is almost anarchistic, you do not know where the next advance is coming from. We did have a general discussion in the Banner Committee in 1993 which was some four years ago. The problem is we have been having these discussions and we had considerable public interest 12 months ago but, as I said earlier, until something like this lamb comes along then really quite frankly the public and the media is not interested because scientific issues are fairly dull and boring and it is only when something like this happens that we manage to capture the public's interest.

Chairman: Either success or disaster.

Dr Williams

166. You said earlier that there are groups in the United States, and you mentioned Paris, which are working in parallel areas. Are there some countries—thinking particularly of Germany—where this type of research would not be allowed?

(*Dr Wilmut*) I am sorry, I do not know.

(*Professor Bulfield*) We can think of no countries that have regulations that are more stringent for working with animals than the UK. Certainly the Animals (Scientific Procedures) Act, and I have worked in three or four countries in the world including the States, is considerably more stringent and careful than any regulations anywhere else that I have come across. Of course, it does not cover the particular point you were making which is the ethical issue. As far as I am aware there is no country anywhere that has a committee to discuss ethical issues in animal breeding. Obviously they do in humans but not in animal breeding.

167. Is that the root of our problem in terms of the publicity over the last week, that the breakthrough you made in Edinburgh in the human mind, and certainly in the tabloid press, is immediately transplanted into the human domain and that in science genetics knows no such boundary and the discoveries that you have made in breeding or animal cloning experiments obviously can be transplanted into humans if any nation or group of people are so minded?

(*Professor Bulfield*) Perhaps the public might have been reassured if there had been an advisory committee like the Advisory Committee on Genetics Modification from which we would have got permission to do this work. In fact, I can tell you now that to do genetic modification on these cells that would not necessarily I believe have to go to ACGM as a special issue because it has already been done on the mouse. In fact, we are putting together a paper now to submit to ACGM to inform them about what we are doing. Our reading of the regulations is that we are not doing anything any different. If we had an advisory committee as was proposed in the Banner Report it is very clear that we would have at least told them what we were doing and they may have had to keep it confidential in a sense if it was prior to filing a patent, or they may not, it just depends at what point the invention was. As we said earlier the invention in this case was at quite an early stage, not at this rather later stage.

Chairman

168. You would have felt that to some extent they were protective between you and the public interest?

(*Professor Bulfield*) Yes. As I said earlier, Chairman, the reason why the scientists were extremely keen to get transgenic animals within the remit of ACGM was because they wanted some forum between them and the public so there could be an informed discussion in a debating format or in a forum whereby many of the public interests were represented.

Dr Bray

169. Professor Bulfield has made the point powerfully for getting broader discussion. In the human genetics field we have the Human Genetics Advisory Commission, in your view would it be a possible step to extend the scope of the Human Genetics Advisory Commission so they would consider matters which were also arising dealing with animal genetics, interacting on some of the possible issues?

(*Professor Bulfield*) I think some of the issues may be so different, particularly when you get into plant cloning. Cloning has existed in plants for a very long time, as has genetic modification. The issues there are in relation to the environment on which there is another Government advisory committee. As I said earlier, I do not feel that there are substantive ethical or scientific issues to consider in using this technology in animal breeding. The Banner Committee felt that as well. However, it is not my view that counts, it is the view of the public. I am not sure whether a committee dealing with humans issues, which are quite considerably different, would be the right forum. I would have to give that a bit of thought.

170. Who would have sufficient authority to persuade the public that implications or applications in the human field from work done in the animal field is not becoming of overriding importance?

(*Professor Bulfield*) I would hope it would be a committee equivalent to ACGM. It is certainly not the scientists themselves. It is clear that our motives are questioned by the public or at least by some commentators interpreting what we do for the public and therefore it would be better for us and better for everybody if it was not the scientists. As I mentioned earlier, I would have felt a lot more comfortable in the last ten days if there was something equivalent to the ACGM between us and the public in this so it was clear we had obtained the required permissions or there was some form of informed debate.

[**Dr Bray** *Cont*]

171. Do either Dr Wilmut or Dr Colman want to comment on that?

(*Dr Wilmut*) I would like to make a comment on the general issue of the discussion of potential applications in the human. I think that we are only part way through the process of education and thinking about it. In fact, somebody associated the writing about human applications with the tabloid press. It is by no means limited to the tabloid press. I am disappointed to see in my view what are unreasonable thoughts for using cloning have actually come from some eminent scientists. It seems to me that if you sit back and think about it most of the suggested applications for copying of a human are actually nonsensical. It is a very distressing situation and I think that some of the comments that have been made had added to the distress of people who are losing a child. The idea that you can bring back a child, the idea that you can bring back your father in one particularly sad case, it is simply nonsensical. You can make a genetically identical copy but you cannot get back the person that you have lost. I am sure there are other suggested uses. I think we are reaching a stage that whilst journalists use these sorts of images to promote the story there is a sense in which they now need to come clean and say really the numbers of uses that actually make any kind of sense are these and discuss them rather than just use these headline grabbing stories.

Chairman: We hope to make a contribution.

Dr Williams

172. Can I come in on one specific application. What about the child who needs a bone marrow transplant and its parents then perhaps want an identical child where there would be no rejection from it.

(*Professor Bulfield*) Chairman, I think these are issues for society, they are not issues for scientists, with respect. I have seen a report in the press of a couple in America who had one child because they were not compatible with the child who required a bone marrow transplant and they had another child who then ended compatible with it. In a way people have already made those decisions. I certainly do not think those are decisions for us and I do not think our opinion on it is any more valuable than anybody else's.

Chairman

173. It is just possible we may make some progress in this area.

(*Dr Colman*) I would like to comment over the public scrutiny. I think this is a very troublesome issue, whether the public have a veto at the one extreme or should be consulted at least before certain experiments are done. It is a troublesome issue because of course scientists would worry about a veto before work has ever been done and success has been achieved. I was reminded last week by the furore going on with the Human Genetics Commission about what the insurance industry will do with genes, the sequences of genes in particular in regard to people who they know have predispositions to particular diseases. In the same week we had four couples taking a local authority to court because they wanted one of the successes of genetic engineering to be exploited, this was the provision of recombinant Factor-8 to their children. I just wonder if you went back to 1953 and asked the public whether they would have approved of Watson & Crick describing the structure of the gene and whether they would have said that this discovery would have been to the benefit of society. I think it is very difficult to ask people before success has been achieved what the potential uses and abuses of that technology will be. That is what I would find a particularly difficult issue in these types of areas.

Mr Miller

174. I would like to move on, if I may, to Roslin's relationship with MAFF perhaps to set the scene. You said at your industry day that you received unanimous support from the animal breeding industry and the Science Minister, Ian Taylor, described your work as a testament to our first class scientists. How much funding actually came from that?

(*Professor Bulfield*) Could I just give a little bit of background. In the mid-1970s institutes like our's were entirely Government funded. Money from the old Agricultural Research Council was moved over to MAFF to fund commissioned research which was in support of the policies of the Ministry of Agriculture.

Chairman

175. Commissioned by MAFF?

(*Professor Bulfield*) Yes, commissioned by MAFF. We are now in a situation in Roslin where we get roughly 50 per cent of our funding in contracts and 50 per cent from Government to support our core research. Of the 50 per cent provided by Government two-thirds is provided by MAFF in commissions and one-third is provided by the BBSRC. The project that Dr Wilmut has been working on is currently—and I say currently because this evolves over a period of years—65 per cent supported by MAFF. The other component is a mixture of industry, we have some funding from PPL Therapeutics, the European Commission because Dr Wilmut is also involved in a European effort in this area, and by the BBSRC. Currently this project is 65 per cent funded by MAFF.

176. Would it have been possible for you to apply to the BBSRC for support for the whole of the project?

(*Professor Bulfield*) Our core funding is allocated to us—full stop. It is up to us to decide how we spend it. Currently the BBSRC core funding is 19 per cent of the whole. I use that funding to support mostly the molecular biology in the Institute, the basic research in the Institute. It is possible for us to apply for funding to the BBSRC Directorates for three year contracts. They would have to be on a specific project. That sort of opportunity is available to us. The difficulty with funding core research on three year contracts is that we have teams which we have

[**Chairman** *Cont*]
built up over a number of years who are led by people like Dr Wilmut who have permanent contracts and that is where we get into some difficulty.

177. According to the press reports MAFF are reducing their contribution by half from 1 April and I think they are cutting it altogether from April 1998. If this research is so important in terms of the animal breeding industry and its particular spin-offs into human genetics, is it not a bit shortsighted of MAFF to withdraw that support? What effect would that have on the research projects you are involved in?

(*Professor Bulfield*) The 65 per cent from MAFF that supports Dr Wilmut's lab is part of these commissions which traditionally have been rolling three year contracts. Over the years MAFF has gradually changed their approach to these and changed them into fixed term contracts. Dr Wilmut had one of these rolling contracts that comes to an end on 31 March 1997. MAFF have indicated that from 1 April as it rolls forward they only wish to provide half the funding of the project which means we have a shortfall of roughly £125,000 and from 1 April 1998 they wish to terminate funding in this area completely. My difficulty is that although I was aware of some of MAFF's feeling about this project, ie that they did not wish to roll it forward in some time around November/December, I only got the formal letter on 27 February which incidentally was the same day that the paper was published in *Nature*. That gives me the best part of a month to try and put together a funding package. Normally what I would do is say: "this project is essential for the Institute" and will move other funds around but, unfortunately, the total package of reduced funding we have got from MAFF this year is somewhere over £600,000 which is roughly 17 per cent of our funding from MAFF so that is going to put me in quite a difficult position. We can deal with changes in policy provided we get plenty of time and provided the cuts or the changes, the swings are not very large. In this case the swing is rather large and the time I have to respond to it actually puts me in quite a bit of difficulty.

178. Yes, but if I was sitting in one of the ivory towers down the road in the Minister's chair, I would say, "Come along, Professor Bulfield. You knew that the funding was short term. We told you way back that this was going to happen and in any case it should be funded by the industry". How would you respond to that kind of attitude coming out of MAFF?

(*Professor Bulfield*) Well, I think the problem is that it indicates how difficult it is with the change of what has been accepted in the past as commission-core funding, and a change of that funding to short-term contracts when you have got teams working on long-term strategic research and also if you are on a short-term contract you are then exposed to changes in policy as the policy groups change in MAFF and different policy people come in with different views, so you are right in saying, and MAFF is right in saying, that legally they are correct, but this is long-term strategic science in the UK and if MAFF does not support the strategic science underpinning the agriculture industry, and you have heard today that we have only produced one animal and we have not applied it to pigs and cattle yet, so there is a lot of work to do, if MAFF does not support that strategic science, then it is difficult for me to know who does.

179. Would you agree with me, therefore, that unless MAFF did or does continue to support this kind of important research, the spin-off technologies and the spin-off companies that are emerging, like Dr Colman's company, for example, would never get the financial confidence of the people that are investing in him?

(*Professor Bulfield*) Well, there is a difficulty here because this technology is generic, to use the modern jargon, and it applies over a wide range of industries. Clearly MAFF do not see their role as supporting Dr Colman's company which is working really in the pharmaceutical industry and one does not expect them to do that. I certainly think that the first applications are in the biotechnology industry, but, as you mentioned, we had an industry day at the Institute also on February 27 when the leading members of the UK animal breeding industry were there, including the Milk Development Council, the Meat & Livestock Commission, the cattle and pig breeding companies, and also members of the Chief Scientists' Group, including Dr Shannon, the Chief Scientist at MAFF, and the industry were unanimously in support of the research in this technology. One commented that it was the biggest breakthrough since artificial insemination and probably bigger. We are aware that we have to do maybe a few more years' work to get this technology to the use of the breeding industry. Now, if I am going to have to go out and find the funds currently from industry, I am going to have to concentrate mostly on the biotechnology industry. If you talk about the animal breeding industry, it is not organised in that way, unless I go to the United States. Now, we have a lead for this technology in this country at the moment. I am not doing this for the benefit of my colleagues or for the benefit of the Roslin Institute; we are supposed to be doing this for the benefit of the UK and I want to see this technology exploited in the UK, not elsewhere, but my major aim in the next few months is to keep Ian's team together. I do not want somebody coming along with a blank cheque and poaching this guy and taking him to California. That is not what I want to happen.

Mrs Campbell

180. I did ask Dr Wilmut a question earlier about the importance of the security of the funding in trying to get this kind of accomplishment. What do you feel are the chances of being able to produce something of similar standing in the next 10 or 20 years given the existing funding regime?

(*Professor Bulfield*) Well, I am a little nonplussed by the funding situation at the moment. It is quite difficult for me to cope with. I have no doubt, it is my intention to keep Dr Wilmut's team together. My main concern is how we apply it to the agriculture industry and not to the biotechnology industry. I think Dr Colman's company is very supportive in that area and there are a number of other biotechnology companies who also are interested in the technology. I am afraid I have not got a simple

[**Mrs Campbell** *Cont*]
answer to that and you are asking me four or five days after I have received a letter which has confirmed that I have got to take some very drastic decisions. In fact in the short term the only decision I can make is to cut costs which means I am going to have to make a significant number of our permanent staff redundant and to use the resources as I feel best within the Institute, so I am going to have to make a number of decisions which are going to be very difficult all round, but I have to protect this work because this work is among the two or three highest priority projects in the Institute.

181. That was not quite what I asked you. I thought that was the gist of my colleague's questioning. What I am concerned about is given the three-year contracts whether it is likely that you will be able to get funding for a research project of a similar nature which may not have any obvious applications at this stage. I think that the sheep planning project is actually now on a different basis and that ten years ago it was precisely at this point where we could not see what the end product was going to be.

(*Professor Bulfield*) Let me give you another example to see if this answers your question. We also are the lead centre in the UK for the farm animal genome mapping programme. These are mapping farm animal genomes which are equivalent to mapping the human genome. We lead on the pig and we jointly lead on the cattle programmes in Europe and we lead the chicken programmes. We have a very high profile in this area. I actually feel that this technology, which we have not talked about today, is going to have far longer-term implications for animal breeding and of course for humans than is something like cloning because it is really opening the black box and we are going to be able to understand the periodic table of life. Now, the funding for this project is put forward together from a whole series of sources. At one point I counted 16 different pieces of funding that I was putting together for this, all of which were in contracts no longer than for three years, and some were shorter than three years. Now, an F2 experiment, a two-generation experiment with dairy cattle takes nine years and it is very difficult to deal with that because this is strategic science; it is not basic, it is not applied. We know it is going to be useful, but we cannot predict where it is going to be useful and, therefore, it is difficult to go to industry because we cannot say that it will do this or it will do that, but we know it is going to have an impact. It is not basic because it is not curiosity driven. It is putting together the building blocks of what we require for the biotechnology and the agriculture industry for the future and this area of strategic science is one that is difficult to handle and the main reason is that three government departments deal with it now. There is the BBSRC, which is of course the DTI, there is MAFF and there is the Scottish Office which has a very large R&D programme, and the three ministries do not really buy into a core five-to-ten-year implementation programme which of course would implement Technology Foresight as well. This is where we need to get ourselves sorted because I cannot go to one person and say, "It is your job to fund genome mapping in the UK". There is no one person I can go to.

182. I think you have explained one other area which might be affected by your funding cuts, Professor Bulfield, but are there any other areas that you are worried about which might be affected by the cuts?

(*Professor Bulfield*) Well, the programme has actually hit three areas. It has hit Dr Wilmut's area, and it has also hit the pig genome mapping programme where we have had a 50 per cent cut and the other area we are having some difficulty with is animal welfare where the cuts are roughly 30 to 35 per cent. Of course I am still at this stage, even though we are very near the 1st April, I am still at this stage trying to work out what all this means and I do not have a clear view.

Dr Williams

183. Is MAFF not likely to change its mind in view of the importance now attached to the publication of your paper?

(*Professor Bulfield*) Well, I understand that the view that MAFF is taking and the Chief Scientists' Group are briefing their ministers on is that they have done what they set out to do and that this technology is not of interest to the animal breeding industry. I have already indicated to you today that I believe this technology is not done and there is quite a bit of work required in not only the sheep, but applying it to other species. I also believe that we have the support of the animal breeding industry and the position with the animal breeding industry is that it is not near enough the market yet that the animal breeding industry is capable of taking it up.

184. Do you think that MAFF is going to reverse its decision?

(*Professor Bulfield*) I would not like to comment on that.

Mr Miller

185. But the effect is that the testament of our first-class scientists, if any change takes place, is that those first-class scientists will be on the scrap heap?

(*Professor Bulfield*) Well, Mr Taylor is a Minister of Science and of course in his remit is the BBSRC which of course does support the Institute and it is not the BBSRC's funding of the Institute that we are having difficulty with this time, no.

Chairman

186. Could I just clarify one point? Does the BBSRC carry the cost of redundancies if you make them?

(*Professor Bulfield*) Yes, any decision made by the Ministry of Agriculture in reducing funding, it is the BBSRC that has to carry that cost. I believe those costs have been running at roughly £5 million a year for the last three to four years and I suspect that the costs will be something higher than that because my colleagues in other institutes have been similarly compromised by similar decisions.

Mr Batiste

187. You are operating in an area where a little downstream from where you are the money generated for those who exploit and develop your product will be enormous and you are holding the patents now for many of these very important seminal discoveries. Do you anticipate a period, assuming the research is followed up, as you hope it will be, whereby you will get very significant financial benefits? If they do flow, are you able to keep them in Roslin or do you have to pass them on? If you can keep them, do you see a time when you can be self-funding?

(*Professor Bulfield*) Well, that is a very interesting and important question. I think Dr Colman has already explained to you that in the area of biotechnology, it can take up to a decade to bring a product to the market and, therefore, even though we have the patents and we have a potential revenue flow, that will take some time in coming. The agreement of the BBSRC with its institutes is that it can keep a considerable proportion of that income.

188. The institutes can?

(*Professor Bulfield*) The institute can keep up to 10 per cent of its turnover presently from any income it generates from patents. I must qualify that because I am not sure whether it is turnover actually or it is grant, but it is one or the other, but it is a considerable proportion of money. Any money over that, I have the possibility of negotiating with the Chief Executive of the BBSRC, so, for example, if I wish to use some of that money to build a building that was over 10 per cent, I could start some negotiations. Now, additionally to that, within the Institute the first piece of any money we get from any patent goes to the scientist. Then there is a complex sliding scale whereby it goes to the scientist's laboratory because quite frankly most scientists want the money in their laboratory and they do not want to be driving around in BMWs, and then that money will go to the department and then to the Institute, so we have a complex sharing scheme within the Institute. I have to tell you that although our first patent was probably logged in about 1987, neither the Institute nor the scientists are managing to get a revenue stream, but of course if Dr Colman's company is successful, then maybe within the next decade the Institute will be in quite a strong position.

189. We were told that in the United States you would not get any revenue stream for at least 10 or 12 years on any new product.

(*Dr Colman*) Yes, but our first product, if everything goes according to plan, is 2001.

(*Professor Bulfield*) And that is the first patent we ever filed in the Institute, so that would be our first one.

Chairman: Thank you very much. Your and your colleagues, in the sense of close commercial ties, Dr Wilmut and Dr Colman, have been with us for an hour and 45 minutes and I do not think for one moment you have lost the interest and to some extent excitement of the Committee. We are very grateful for the candour with which you have discussed not just your project and its consequences, but for the way in which you have answered the questions which relate to funding and the organisational arrangements between you and Dr Colman and his particular company. I think this Committee would be right to say that we are extremely impressed by what you do and we are extremely grateful for the clarity with which you have exposed what you do and have answered the many questions we have put before you today. Thank you very much indeed.

APPENDICES TO THE MINUTES OF EVIDENCE

Memorandum submitted by the Home Office (CLE 2) (6 March 1997)

ROSLIN EXPERIMENT

Introduction

The Committee has asked for a memorandum setting out the regulatory system which applies to the Roslin Institute experiment and other research on animal cells and/or embryos.

The Animals (Scientific Procedures) Act 1986

2. The Animals (Scientific Procedures) Act 1986, which is administered by the Home Office, regulates experimental and other scientific procedures applied to protected animals and which may have the effect of causing them pain, suffering, distress or lasting harm.

3. Protected animals are defined as living vertebrates other than man plus one invertebrate species, *Octopus vulgaris*. The foetal, larval or embryonic form of any protected animal is also protected from a given stage of development. In the case of mammals, birds or reptiles, this is from the elapse of half the gestation or incubation period. In any other case, this is when the animal becomes capable of independent feeding. Anything done at an earlier stage of development which may cause adverse effects at these later stages is also regulated.

4. Regulation extends to any scientific procedure for the purpose of, or liable to result in, the birth or hatching of a protected animal, if it may cause pain, suffering, distress or lasting harm.

5. In terms of cloning or other similar work on animal cells or embryos, the definition of a regulated procedure therefore covers almost any procedure, performed for an experimental or other scientific purpose, which is likely to cause pain, suffering, distress or lasting harm to the adult animals or which may lead to the birth of an animal (or its development beyond the mid-gestation period or independent feeding stage) which may itself experience one of these adverse effects.

6. Excluded from the definition of a regulated procedure is any recognised veterinary, agricultural or animal husbandry practice. The Royal College of Veterinary Surgeons determines whether a procedure is a recognised veterinary practice. Any procedure exempted from the controls of the 1986 Act for this reason would fall under the controls of the Veterinary Surgeons Act 1966.

7. Under the terms of the Animals (Scientific Procedures) Act 1986, those carrying out regulated procedures must hold a personal licence; the work must be authorised in a project licence; and the place where the work is carried out must normally have a certificate of designation. Control over the type of work that can be carried out is exercised primarily through the project licence. An application for a project licence must describe: the background, objectives and potential benefits of the work; the plan of work; and the procedures to be carried out (including the species of animal to be used, an estimate of how many animals are needed, their stage of development, the likely incidence and nature of possible adverse effects and methods of prevention or control of such effects).

8. In determining whether, and on what terms, to grant a project licence, the likely adverse effects have to be weighed against the benefits likely to accrue from the work. A licence will not be granted unless the applicant has given adequate consideration to non-animal alternative means of achieving the purpose of the work. A high premium is placed on what are recognised as the "3Rs": if alternatives cannot be found for protected animals (replacement), then reducing the number of animals needed (reduction) and the likely adverse effects (refinement).

9. Project licences last for a maximum of five years. If the work is to continue, then a fresh application must be made. In considering all applications, the advice of specialist inspectors is provided. Further advice may be obtained from independent assessors or the Animal Procedures Committee, a statutory body set up under the Act to advise the Secretary of State on matters concerned with the Act and his functions under it.

10. Section 24 of the 1986 Act prohibits any person, otherwise than for the purpose of discharging his functions under the Act, from disclosing information obtained in exercising those functions where there are reasonable grounds for believing it was given in confidence.

Other Relevant Legislation

11. Any genetic modification of cells or embryos would also be subject to the Genetically Modified Organism regulations administered by the Department of the Environment. The cloning of livestock is also covered by the Animal Health and Welfare Act 1984 administered by the Ministry of Agriculture, Farming and Fisheries.

The Work of the Roslin Institute

12. Work resulting in the cloning of a sheep ("Dolly") by Dr Ian Wilmut of the Roslin Institute in Scotland was published on 27 February in the magazine "Nature". Similar articles from the same source appeared last year and described cloning which involved the use of a nucleus obtained from cells grown from an early sheep embryo. In the case of "Dolly", the cloned nucleus was obtained from DNA material from the udder of a mature animal.

13. Essential elements of Dr Wilmut's work (including the harvesting of DNA material from the donor animal and the implantation of the clone cells into the surrogate mother) are licensed by the Home Office under the Animals (Scientific Procedures) Act 1986.

14. The primary purpose of Dr Wilmut's work has been to investigate the mechanisms that regulate early mammalian development and to use that new knowledge, including developments in the nuclear transfer technology, to establish novel procedures for the artificial breeding of agricultural animals. The purpose specified in the licence application was not to develop technology for the cloning of humans.

15. So-called genetic engineering in animals has been in progress for at least 15 years. The potential benefits from genetically modified animals include:

- — increased productivity—more meat, milk or eggs;
- — increased resistance to disease or other adverse conditions which might affect the animal;
- — production of pharmaceutical substances;
- — fundamental study of mammalian biology;
- — modelling human disease, aiding research into new or improved therapies;
- — possible future provision of organs for xenotransplantation.

Successful cloning techniques would allow the rapid multiplication of elite or modified animals. They also have the potential to save endangered species from extinction and for providing a possible means for studying the ageing process.

16. Developmental work has been conducted mostly in cell culture in the laboratory without the use of living animals and therefore without the need for licence authority under the 1986 Act. This established that "nuclear transfer" had the potential to produce viable cell aggregates in culture. For *in vivo* stages, licence authority has been given for studies to validate that the systems can be made to work in practice.

17. "Dolly" appears to be a normal healthy animal. There is no evidence to date of pain, distress, suffering or lasting harm as defined in the 1986 Act but minor surgical interventions were performed on the adult animals (those donating tissue and receiving the embryo). Outside the scientific orbit of the project, such techniques could be allowed by the Veterinary Surgeons Act 1966. "Dolly" represents the only success from 277 attempts. It is understood that none of the other 276 attempts led to a foetus developing past the mid-period of gestation. The costs in terms of the cost-benefit analysis required by the 1986 Act are therefore relatively modest.

18. Dr Wilmut's current project licence also authorises development of this work to cattle and pigs. Only sheep work has been pursued with any success to date. The early technical problems encountered with the other species, and the poor success rate, support the belief that the technology has some way to go before it could be applied more widely. A separate strand of this research, however, has cast light on factors responsible for large calf syndrome—where calves produced by *in vitro* fertilisation (IVF) become too large, causing serious problems at birth.

19. It is understood that Dr Wilmut currently has no immediate plans to use further adult DNA material for nucleus transfer. His project licence, however, remains valid and he could therefore, recommence such work without further Home Office approval.

Related Work

20. The basic technology on which Dr Wilmut's work has been based, nuclear transfer, has already been applied for commercial purposes elsewhere within the UK but outside the controls of the Animals (Scientific Procedures) Act 1986. In these cases, the work fell under the Veterinary Surgeons Act 1966 because it was not conducted for scientific purposes and because it employs recognised veterinary, agricultural or animal husbandry practice.

Memorandum submitted by the Department of Health (5 March 1997) (CLE 3)

Background

1. On 27 February the scientific journal *Nature* published a paper describing research on a cloned sheep (named "Dolly"): the research was co-funded by MAFF. A paper published last year on the same subject also attracted considerable publicity. Publication of the article has raised questions about cloning human cells to

generate further embryos. The President of the USA and the President of the European Commission are both reported to have ordered investigations into the implications for humans of the outcome of the sheep cloning research.

Cloning

2. Cloning may be defined as the production of a number of cells from a single cell from an individual to produce another genetically identical individual. This can be achieved in one of two ways. *Nuclear transfer* involves the transfer of a nucleus of one cell to a cell taken from another person or embryo. The alternative is *splitting* cells from an embryo at the 2–8 cell stage to produce more embryos. Identical twins are naturally occuring clones. They arise when an embryo splits in two.

3. There is no evidence that cloning human embryos by any method has taken place in the UK (although we understand that it has been done in the USA on an experimental basis).

Cloning and the Human Fertilisation and Embryology Act 1990

4. Discussion of the relevant sections of the Act are at *Annex A* which sets out the restrictions applying to experimentation on embryos.

5. As with the Warnock Committee Report (1984) and the subsequent White Paper (1987), the Human Fertilisation and Embryology Act 1990 anticipated the possibility of cloning. It forbids any procedure involving nuclear transfer *by replacing a nucleus of a cell of an embryo . . .* In the case of the sheep it appears that cloning took place by replacing nuclei into egg cells rather than into cells of embryos. However, the Act also provides that "no person shall bring about the creation of an embryo except in pursuance of a licence". This means that (subject to what is said in paragraph 6 below) whichever approach to cloning is adopted, the procedure is either illegal or cannot be carried out without a licence from the Human Fertilisation and Embryology Authority.

6. The committee has raised a question relating to the adequacy of the Human Fertilisation and Embryology Act 1990 to govern cloning techniques such as those used to clone "Dolly". The Committee's doubt hinges on the definition in the Act of "embryo". It is possible that the definition used in the Act does not, in fact, include an "embryo" produced in this way. If this were the case then the HFEA may have some difficulty in relying on the Act to regulate cloning of humans using this particular technique.

7. As the Committee is aware, we have agreed with the HFEA a joint approach to Counsel on the definition of "embryo" as used in the Act. Our current legal advice is that if a court were asked to consider the matter is would be likely to come up with a broad construction which would bring the technique used in the cloning of "Dolly" within the Act. In practice, the opportunity has not arisen since 1990 for this to be tested in the courts.

Conclusion

8. Our concern is to ensure that measures introduced by Parliament in the Human Fertilisation and Embryology Act 1990 are not evaded by developing technology. In the case of cloning, techniques involving nuclear transfer were specifically banned by the 1990 Act in terms which may not wholly match recent advances in this field.

9. The Warnock Report (1984) recognised that public anxiety about techniques involving cloning centres not so much on their possible therapeutic use but on the idea of the deliberate creation of human beings with specific characteristics. They recognised that cloning by nuclear substitution would raise more fundamental questions and recommended that the HFEA should promulgate guidance on what research in this area would be unlikely to be considered ethically acceptable, and envisaged such guidance being reviewed from time to time to take account of both changes in scientific knowledge and changes in public attitudes.

10. There are, or will be, areas where there may be a positive therapeutic role for research in this area, particularly in the field of genetics. A total ban on such techniques could affect research that does not involve cloning as such and would have the potential to prevent research into a number of crippling or life-threatening inherited illnesses in humans (the "mitochondrial diseases" such as some forms of encephalomyopathy, cardiovascular disease and type II diabetes). Should any change to the legislation be indicated these consequences would need to be considered. Our favoured approach is to adopt the principle proposed in the Warnock report and continue to adapt regulation in this area rather than impose an outright ban.

Annex A

CLONING: RELEVANT SECTIONS OF THE HUMAN FERTILISATION AND EMBRYOLOGY ACT 1990: RESTRICTIONS APPLYING TO EXPERIMENTATION ON EMBRYOS

Section 3(3)(a) and (4)

1. The starting point is section 3(3)(a) which prohibits the keeping or using of an embryo after the appearance of the "primitive streak". This has to be read with section 3(4), which in effect explains how that phrase is to be interpreted. The primitive streak "is to be taken to have appeared not later than the end of the period of 14 days beginning with the day when the gametes were mixed", this being the origin of the 14 day limit.

2. And in calculating the time from the mixing of the gametes to the appearance of the primitive streak or 14 days, which ever is earlier, any time during which the embryo is stored is not counted when calculating the 14 days.

Section 15

3. This section imposes general conditions in respect of research licences, relating to records and information and, more importantly for present purposes, provides that "no embryo appropriated for the purposes of any project of research shall be kept or used otherwise than for the purposes of such a project". That is, embryos which are to be used for a particular research project can only be used for that project. They cannot be used in a different project, either instead of, or as well as, in the one for which they were appropriated.

Schedule 3

4. Paragraph 2(1) provides that a consent for use of an embryo must specify one or more of three specified purposes, including, at (c), use for the purposes of a project of research.

5. Paragraph 2(2) requires all storage consents (which includes any storage for research purposes) to specify the maximum period for storage, state what is to be done if the person giving the consent dies or becomes incapacitated (ie before the embryo is used for the purpose for which it is being stored). The consent may also specify conditions subject to which embryos may remain in storage. The maximum period for storage is that imposed by section 14(4) of five years and the extension of the storage period provided for in regulations applies only for treatment, not research.

6. Paragraph 2(4) provides that consent may apply to the use or storage of a particular embryo or, in the case of a person providing gametes, to the use or storage of any embryo created using those gametes. Where a person has provided gametes the terms of the consent may be varied or may be withdrawn, either generally or in relation to a particular embryo. All the above provisions are to ensure that a person gives an effective consent for the use of any embryo, including for research.

Schedule 2—paragraphs 3 and 4

7. Schedule 2 sets out the parameters within which all licences are granted. Paragraph 3 deals with research licences. It is these provisions which impose the significant restriction on what may be done by way of research.

Paragraph 3(1)

8. Under paragraph 3(1) research licences may authorise two things; the creation of embryos in vitro, and the keeping or using of embryos, but only for the purposes of the research project specified in the licence.

Paragraph 3(2)

9. Paragraph 3(2) operates as an express limitation on the types of research which may be undertaken. A licence granted under paragraph 3 cannot authorise any activity unless it appears to the HFEA to be necessary or desirable for certain specified purposes. These are:

(a) promoting advances in the treatment of infertility

(b) increasing knowledge about the cause of *congenital* disease

(c) increasing knowledge about the cause of miscarriages

(d) developing more effective techniques of contraception

(e) developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.

10. Thus the activities for which licences may be granted are all broadly connected with human reproduction or problems present from birth. "Congenital" is emphasised above because it is clear that this imposes limitations on the kinds or research into disease which can be undertaken ie only congenital disease, not other kinds.

PARAGRAPH 3(3)

11. The words at the end of paragraph 3(2) provide that other purposes may be specified in regulations. Paragraph 3(3) then imposes a limitation on what those regulations might provide for. Research projects would only be able to be authorised under such regulations if they increase knowledge about the creation and development of embryos, or about disease, or to enable such knowledge to be applied. For example, the restriction to research on congenital disease imposed by paragraph 3(2)(b) would not apply, so projects of research into other diseases would be possible.

PARAGRAPH 3(4)

12. Paragraph 3(4) provides that no licence can authorise altering the genetic structure of any cell while it forms part of any embryo, except where this is specified or determined in accordance with regulations.

PARAGRAPH 3(6) AND (7)

13. Before granting a licence the HFEA has to be satisfied that any proposed use of embryos is necessary for the purposes of the research ((6)) and, subject to the provisions of the Act, licences granted under paragraph 3 can be made subject to conditions specified in the licence ((7)). Both of these subparagraphs are thus capable of being used to impose restrictions on the research use to which embryos may be put.

PARAGRAPH 4

14. This applies to all licences granted under Schedule 2, whether for treatment, storage or research. Subparagraph (1) provides that a licence can only authorise activities to be carried out on premises which are specified in the licence and under the supervision of "an individual" ie a human person, not a corporate person, designated in the licence. Subparagraph (2) sets out what a licence cannot do. It cannot authorise activities which fall within both paragraph 1 (treatment) and paragraph 3 (research). It cannot apply to more than one research project or authorise the carrying out of the activities by more than one individual and nor can it apply to premises in different places.

REGULATION MAKING POWERS IN PARAGRAPH 3

15. These have not yet been exercised. That is, the possibility exists for extending the purposes for which a research licence could be granted (paragraph 3(2) and (3)), or for licences to permit the altering of the genetic structure of a cell while it forms part of any embryo (paragraph 3(4)).

16. However it would be a decision for the Secretary of State as to whether or not to exercise either of these powers. Further, section 45(4) of the Act provides that in respect of any regulations made under paragraph 3 of Schedule 2, regulations cannot be made unless a draft has been laid before both Houses and approved by resolution of each House (ie the affirmative procedure). In this way, any regulations which would extend the provisions of paragraph 3 would be subject to a full debate in Parliament.

Letter and Memorandum submitted by the IPMS (6 March 1997) (CLE 4)

BIOTECHNOLOGY AND BIOLOGICAL SCIENCES RESEARCH COUNCIL BRANCH
ROSLIN INSTITUTE (EDINBURGH) SECTION

I understand that the Science and Technology Select Committee will meet on Thursday 6 March to consider the implications of the recent cloning of an adult sheep. I further understand that the Committee will also consider the way in which such research is funded.

I chair the Roslin Institute section of the Institution of Professionals, Managers and Specialists (IPMS) which is the trade union that represents the Institute's scientific and technical staff.

Last week was one of very mixed fortunes for the Roslin Institute and its staff. We marvelled at the scientific breakthrough announced by Dr Ian Wilmut's group. However, we were dismayed by the arrival of a letter from the Ministry of Agriculture, Fisheries and Food (MAFF) which provided further clarification of the reductions in MAFF support for research at the Institute.

A MAFF spokesperson has said that we are being disingenuous in presenting these changes in MAFF funding as cuts. This spokesperson is correct in as much as each of our MAFF research contracts has a declared end date and offers no guarantee of MAFF support for follow-up studies.

However, the changes in the way in which MAFF funds research raises fundamental questions and problems for the future viability of BBSRC research institutes and the career prospects of BBSRC staff. In the attached paper we have detailed some of these questions.

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1. Introduction

A number of questions are posed that we consider are relevant to the Select Committee's interest in how research such as the sheep cloning project are funded and selected for funding. We suggest that the Select Committee may wish to seek answers to these questions from MAFF, BBSRC and others. We offer our perspective/answer to some of these questions. We also provide some background information relevant to these questions.

2. MAFF Funding or Research

In this section, we highlight changes in the nature and extent of MAFF funding of research.

MAFF funding of research in BBSRC institutes

In order to understand the nature of the changes it is necessary to consider the history of MAFF funding of research in BBSRC institutes. Following the 1972 White Paper on a "Framework for Government Research and Development", 55 per cent of the funds of the then Agriculture Research Council (ARC) were passed to MAFF. [ARC evolved during the 80s to become the Agricultural and Food Research Council (AFRC) and eventually a major component of the Biotechnology and Biological Sciences Research Council (BBSRC) in 1994.] It was anticipated that MAFF would use these funds to purchase research from ARC institutes. This arrangement worked successfully for many years with MAFF "commissioning" research from scientists based in ARC research institutes. MAFF research commissions were seen as long term stable sources of research funding. Each MAFF Commission covered a broad area of research. The research objectives within each area were subject to periodic review that allowed the research programme to evolve to recognise changes in priorities and/or science. The institute staff engaged in these research commissions were employed on "permanent" research council contracts, identical to those of their colleagues engaged in research projects funded from the block grants (from the Science budget as administered by the research council) to the institutes. These arrangements provided stable long term funding for strategic agricultural research during the 70s.

MAFF demonstrated a clear commitment to long term support of strategic agricultural research and to the maintenance of both the necessary teams of scientists and the capital infrastructure such that the commissioned research budgets included contributions to the ARC/AFRC's capital building and equipment budgets. Thus, MAFF funding was seen as part of the "core funding" of ARC/AFRC/BBSRC research institutes.

Reductions in MAFF support for research in BBSRC institutes

The decline in MAFF support for research in AFRC/BBSRC institutes has been more marked than the general decline in support for agricultural research. MAFF's contribution to AFRC was reduced from £51,755,000 in 1986–87 to £34,760,000 in 1994–95. Clearly, if the latter figures were corrected to 1986–87 prices the decrease would be even more dramatic. These changes are illustrated on the enclosed graphs* extracted from the AFRC 1992–97 Corporate Plan. [The BBSRC's income in 1996–97 in cash terms is not radically different from the projections shown despite the addition of the Biotechnology division of the former Science and Engineering Research Council (SERC)].

MAFF's contribution to AFRC/BBSRC has declined faster than MAFF's R&D budget

Has MAFF's R&D expenditure in its Departmental research laboratories declined, remained stable or increased over this period (1986–97)?

In other words has MAFF protected its own research facilities at the expense of the AFRC/BBSRC?

* Not printed.

Whilst, MAFF's R&D budget has reduced in real terms over the period 1986 to 1995, it increased in cash terms. [MAFF's R&D expenditure was £118.4 million in 1986–87 and £137.2 million in 1994–95.] The proportion of MAFF's R&D budget spent on research conducted in AFRC/BBSRC institutes has fallen from 44 per cent in 1986–87 to only 25 per cent in 1994–95. Thus, it is clear that AFRC/BBSRC has borne a disproportionate share of the reduction in MAFF's R&D expenditure. However, as MAFF also supports research in Universities and Colleges, we do not know what has happened to its funding of work in its own research facilities.

Reductions in MAFF funding of research at the Roslin Institute

Although the start of the next financial year is less than a month away, we still do not know the full extent of MAFF funding for research at the Roslin Institute in 1997–98. For several prospective projects it is still not clear whether MAFF will provide funding or, if it does, at what level. Although there is still considerable uncertainty, it is likely that total MAFF funding for Roslin will be up to £600K less in 1997–98 than in 1996–97. As most of the staff engaged on MAFF-funded research have "indefinite contracts", for the reasons outlined above, redundancies, including compulsory redundancies are inevitable.

These cuts are the latest in the steady erosion of "permanent" jobs in agricultural research which started with the attempt in 1981 to cut the Animal Breeding Research Organisation's (ABRO) budget by 80 per cent. Since then about 280 (out of 450) jobs have been cut at the Roslin Institute and its predecessors (ABRO, the Poultry Research Centre and the Institute of Animal Genetics).

The uncertainty about MAFF funding barely a month before the new financial year commences creates severe problems. The costs of redundancy payments, including pay during the period of notice will make significant demands on the BBSRC science budget. The Institute does not have reserves that would allow it to continue paying staff during the period between the ending of their MAFF funding and the securing of alternative funds through the normal grant application procedures.

The customer-contractor relationship

Would the return of the "Rothschild" settlement from MAFF to BBSRC allow the contractor-customer relationship to be restored?

The transfer of funds from the ARC to MAFF in the early 1970s was designed to establish a customer-contractor relationship. It was envisaged that MAFF would fill the customer role with ARC (AFRC) institutes acting as contractors. The concern prior to this so-called Rothschild settlement was that it was inappropriate for ARC to be both a research funder and a research provider. Although these arguments were made in the early 1970s they have echoes in current government policies to separate customer and contractor functions. It is therefore ironic that whilst ARC's successor BBSRC spends a declining share of its science budget income in its own research institutions, the so-called customer MAFF may be spending an increasing proportion of its R&D budget in its own laboratories. [It was AFRC policy from the mid-1980s to increase the share of its science budget income spent in Higher Education Institutions (HEIs)].

MAFF's relationship with its former research institutions

With the privatisation of some MAFF research institutions or their transfer to an arms-length agency status some of the questions now become—

To what extent has MAFF offered guaranteed research income/contracts to ADAS and agencies which were former MAFF institutions?

Have such guarantees been offered to underwrite the financial future of these privatised research organisations?

If such guaranteed contracts have been offered/granted, do they not fly in the face of the government's and MAFF's commitments to open competition between research providers?

3. How are Projects Selected for Funding?

We understand that the Select Committee is interested in the decision making procedures used in allocating funding to projects such as the sheep cloning work at Roslin. We have taken this opportunity to broaden the scope of that question to the generality of the selection of research projects.

Funding decisions—Research Councils

How are research projects selected for funding by the Research Councils?

Research proposals submitted to the Research Councils, including BBSRC, are subjected to scientific peer review as follows.

An outline proposal may be submitted and evaluated for its scientific potential and/or fit with an agreed Research Council policy or specific programme. This screening evaluation is carried out by Research Council central office staff, programme coordinators/managers, members of Research Council research committees, external referees or combinations thereof.

When a full application is received it will be subjected to scientific review by external referees (so-called peer review). The referees' reports (excluding the grading of the proposal) will be passed to the applicants who have an opportunity to respond to criticisms and to address the issues raised. The referees may be given an opportunity for further comment. The proposal is then presented to the relevant Research Council research committee. One or two members of the committee will introduce the proposal, comment on the referees assessments and recommend a grading of the application. The highest ranking proposals will be recommended for funding.

In addition to scientific excellence, some committees, such as the BBSRC's Agricultural Systems Directorate take other factors into account when ranking grant applications. These other factors include relevance to an agreed scientific strategy, links with the relevant industry and the likely contribution of the project to wealth creation and the enhancement of quality of life. Thus, socio-economic factors are also considered.

Funding decisions—MAFF

How does MAFF select research proposals for funding?

How are projects to be carried out at Experimental Husbandry Farms evaluated?

Are different evaluation procedures used for MAFF-funded projects carried out in MAFF's own or former facilities and those carried out be external contractors such as the HEIs and BBSRC research institutes?

Less in known about the procedures that MAFF uses for evaluating applications for research funding. We understand that MAFF uses referees and review meetings to which applicants and relevant experts are invited. There are two elements to MAFF decision making—scientific advisers propose and policy makers decide.

However, no member of staff at the Roslin Institute has been asked to referee an application for MAFF funding. In contrast, many members of staff have reviewed grants applications to BBSRC, the Medical Research Council, the Wellcome Trust and overseas funding agencies including the EC. Similarly, although several members of Roslin staff serve (or have served) on BBSRC and MRC scientific committees, none have served MAFF in an analogous manner. Thus, the extent to which MAFF uses external referees and scientific research committees remains unclear.

Feedback to applicants for MAFF funding is limited. For example, no feedback has been received concerning the scientific content of an application for further studies in pig genome mapping submitted to MAFF in autumn, 1996. The only response has been that MAFF would consider funding pig genome research at half the level requested but with no comments on the content of the proposal.

Timescales

The timescale from an initial idea, through the preparation of an application and its evaluation to the start of a research project can take up to a year. Thus, new research funding cannot be secured at short notice to cover the effects of funding cuts or the rejection of earlier applications. If one would like to develop a new project to follow on from a current three year project, one needs to commence the application procedure at least 12 months before the current project ends.

4. How can Scientific Success be Translated into Commercial Success?

The 1993 White Paper on "Realising our Potential—A Strategy for Science, Engineering and Technology" was particularly concerned with the UK's supposed poor record at turning its scientific successes into commercial successes. Here we consider some aspects of this wealth creating transition.

The penalties of success

Two of the areas of research for which MAFF currently propose to cease funding at the end of the present contracts can be considered victims of their own success. Some of the other work which we had expected to be underpinned by continuing MAFF funding, explicitly expects to be at an equivalent stage (ie. between basic strategic science and application) within a few years.

First, the sheep cloning work (the "Dolly" project) of Dr Ian Wilmut's group. This project currently receives £250,000 per annum from MAFF and was due to end in March 1997. MAFF are currently considering an application to extend the programme for one year only at half the level of funding (ie £125,000). MAFF have discouraged applications for continuation of the nuclear transfer programme on

a longer term basis. MAFF are suggesting that it is already time for the relevant industries to be funding any continuing research.

The results are likely to find an application in the biotechnology sector in the short to medium term and in agriculture in the longer term. There are still many years research required in order to improve the efficiency of nuclear transfer, to determine whether it is possible to genetically modify the cultured cells prior to nuclear transfer and to examine whether the technology will work in other species, specifically pigs and cattle. This research programme combines both basic and strategic research, rather than applied research. Thus, this type of research programme should surely attract support from public funds. Although PPL Therapeutics plc have and will presumably continue to support this work, their interests are limited to specific aspects of the technology. If PPL is the only source of funding, then the full potential of this technology will not be realised in the UK. Rather it is likely that the UK's lead will be lost and the research (and perhaps its practitioners) transferred overseas. UK plc will then have to buy in the developed technology—a familiar and lamentable scenario.

The second example concerns ascites (heart damage) in poultry. This problem costs the UK poultry breeding industry £24 million per annum. The costs on a worldwide basis are $1,000 million per annum. Roslin scientists have adapted a method used to diagnose heart damage in humans to detect the damage caused by ascites in chickens. The scientists have published their findings from 1994 onwards, while engaging in discussions on technology transfer with the pharmaceutical company that developed the human diagnostic kit and with the poultry industry. There are difficulties on both industrial fronts. The pharmaceutical company would find it difficult to justify the current cost of the human diagnostic kit if it produced a markedly cheaper version for mass use in poultry. The poultry industry says that it needs more work on developing the technology and experimental evidence of the feasibility of its use as part of a genetic solution to the problem.

MAFF are not renewing funding for the Roslin group that have made this significant contribution to controlling ascites. MAFF agrue that the ascites work is now complete and that the industry should fund future developments. However, the detection of ascites was only a part of the work included in the applicaton for future MAFF funding. The absence of a funding source to bridge the gap between the initial scientific research and the application or product development is a serious gap in the mechanism for translating science into application.

From science to application

Where are the boundaries between public sector funding of science and the industrial funding of applications?

Are appropriate funding mechanisms and agencies in place in order to support the transition between science and application?

Do the ADAS Experimental Husbandry Farms fill the gap between science and application in an agricultural context?

Who funds work at the ADAS Experimental Husbandry Farms?

Is there a need for equivalent structures to facilitate the transition of biotechnology research from the laboratory to application?

The role of the ADAS Experimental Husbandry Farms (EHFs) would appear to be concerned with filling the gap between basic and strategic agricultural research on the one hand and application on the other. Thus, the EHFs should be operating nearer the market place than the BBSRC research institutes. If MAFF increasingly expects pre-competitive research carried out in BBSRC research institutes to be partially funded by the relevant sector of industry, then this implies that industry funding of work at the EHFs should be proportionately greater than at BBSRC institutes.

5. The Need for Long-Term Funding

The Technology Foresight exercise that was spawned by the 1993 White Paper on "Realising our Potential—A Strategy for Science, Engineering and Technology" has been correctly used to develop a long-term strategic view of the nations's needs and the prospects for science to meet these needs. Unfortunately, although Technology Foresight has developed a long-term view of where UK science should be going, the trend in research funding has continued to be towards increased short-term funding at the expense of long-term support of research centres. This mismatch is as true in the HEI sector as it is in the BBSRC institutes.

Prior Options-the unanswered questions

The recent Prior Options review of Government Research Establishments concluded that the BBSRC research institutes were required. Clearly, IPMS members not only at Roslin, but throughout the BBSRC welcome this conclusion. However, the actions of both BBSRC and MAFF in reducing research funding of BBSRC research institutes is undermining the long-term viability and stability of these institutes.

Therefore, we conclude that the Prior Options review did not properly address the question of how such important national research centres should be funded.

Increases in short termism

Who should fund the "being there", overhead and infrastructure costs of BBSRC (and other) research institutes?

What level of support should such block "being there" grants provide—in terms of facilities, scientific, support and administrative staff and running costs?

In the past, both science budget funding (now termed the Competitive Strategic Grant) and MAFF funding (through Commissions) were regarded as providing the "core funding" of agricultural research institutes. Accordingly, staff employed with these funds were engaged on "indefinite contracts". It was also assumed that these funds provided the "being there" or overhead costs of the research institutes. The switch by MAFF from open-ended research commissions to three-year research contracts suggests that MAFF no longer sees itself as being responsible for the continuing strategic research base in BBSRC institutes. [MAFF commissions are also now effectively three-year research contracts.] Any new staff engaged to undertake MAFF-funded research are likely to be engaged on short-term contracts.

BBSRC is also contributing to the reduction in "permanent" research posts. The BBSRC research institutes are currently engaged in a research assessment exercise which compares the institutes' past performance and their future (science budget funded) research plans. The proposed outcome is that any institute could win or lose (over a four-year period) up to 20 per cent of its Competitive Strategic Grant (CSG). As BBSRC's total CSG is a fixed resource, Institutes that "lose" will be required to lay off "permanent" staff. Institutes that are classed as "winners" are likely to recruit new staff on short-term contracts, as there will be a further research assessment exercise in three or four years' time. Thus, the proportion of staff engaged on "indefinite contracts" will continue to decline. BBSRC is further exacerbating this trend by reducing all institutes' CSG funding each year so that institutes can "buy into" some of the BBSRC's competitive grant systems.

Stability and competition—are they mutually exclusive or can they be synergistic?

Competition between research groups makes a useful contribution to scientific progress. Not only is science a highly competitive activity, but new scientific theories and methods only gain widespread acceptance once they have been shown to be reproducible in the hands of different laboratories. Thus, competing funded research groups are good for science.

We accept that competitive research funding also makes a contribution to science, especially in the development of new ideas and approaches. However, continuity and stability is also essential for science. Continuity of funding allows the development of teams and centres of excellence.

The strength of BBSRC institutes lies in their range of scientific disciplines and the experience of their staff, not only technical expertise in their own area, but knowledge of a range of collaborative disciplines. This enables the flexible formation of inter-disciplinary teams to respond to new opportunities as they arise.

Long-term funding of research establishments and their staff provides greater flexibility than three-year project grants and short-term contracts of employment. Staff employed on three-year projects are engaged to meet specific objectives set out in the grant application in a given time frame, and are thus not available to develop new lines of research which might compromise the project objectives. Permanent staff working in broader areas of research have greater freedom and scope, and a greater range and depth of knowledge to develop new activities. Their accumulated knowledge is the major resource of the research institutions.

Thus, a balance needs to be struck between underpinning long-term support for research institutes and competitive research funding. Developments in recent years driven by changes in policy by both the BBSRC and MAFF are favouring the latter at the expense of the former. It is now time to examine whether the viability of BBSRC research institutes is being compromised by the much reduced proportion of their income that can be considered long term.

Competition must be fair

Whilst we are content to compete with other research organisations, we are concerned that the playing field is not level. For example, the salary costs of a university-based project leader are covered by block grants to the university for teaching and/or research. In contrast, BBSRC-based project leaders are required to ascribe the relevant proportion of their own employment costs to the prospective research contract. It is self-evident that BBSRC research institutes appear to provide less value for money in these circumstances, although of course the university project leader's salary is being met from a different part of the public purse.

6. Concluding Remarks

These concerns with long-term stability and continuity are not merely about protecting the jobs of IPMS members in BBSRC research institutes. These questions about stability are central to the future health of the UK biotechnology and agricultural research sectors and the industries that they underpin. The next industrial revolution will be dominated by biology. This assertion is recognised amongst the conclusions of the Technology Foresight exercise. The biotechnology revolution is highly dependent on developments in

science. Thus, it is essential for the nation's future economic well-being that the UK has a well-funded research base, staffed with well-motivated scientists with appropriate support and facilities.

Statement by J B Gurdon (6 March 1997) (CLE 5)

CLONING EXPERIMENTS IN AMPHIBIA

1. The first successful nuclear transfer experiments were described by Briggs and King (1952, Proc Nat Acad Sci US *38*, 455-463). These experiments were carried out with *Rana pipiens*, and the embryos obtained were not reared beyond a tadpole stage.

Paragraphs 2–6 that follow refer to work using Xenopus laevis.

2. The first cloned vertebrates to become fertile adults were described in 1962 (Gurdon, J B 1962, Devel Biol 4, 256–273 "Adult frogs derived from the nuclei of single somatic cells").

3. At the same time, a publication first showed a clone of multiple genetically-identical frogs (Gurdon, 1962, J Heredity 53, 4–9). A later publication (Gurdon, 1977, Proc Roy Soc B 198, 211–247. Croonian Lecture: Egg cytoplasm and gene control in development.) showed a more visually impressive clone of albino frogs derived from a wild-type (dark green) mother (see attached extract).

4. The first clear evidence that differentiated somatic cell nuclei contain a full range of developmental genes (pluripotency) was published in 1962 (Gurdon, J Embryol exp Morph 10, 622–640); feeding tadpoles were obtained from nuclei of intestinal epithelium cells.

5. The first demonstration that differentiated somatic cell nuclei have a complete complement of genes (totipotency) was published in 1966 (Gurdon and Uehlinger, Nature 210, 1240–1241. "Fertile" intestine nuclei.). This described fertile adult frogs obtained from nuclei of larval intestine.

6. A further, more detailed, description of pluripotent nuclei was published in 1975 (Gurdon, Laskey, and Reeves, J Embryol exp Morph 34, 93—112) showing that nuclei from keratinised skin cells of adult frogs could be transplanted to produce feeding larvae. These experiments demonstrated the general principle that the differentiation of cells involving selective gene expression does not require the loss or irreversible inactivation of genes.

7. The frog work referred to above did not succeed in generating an adult animal from the nuclei of cells of an adult animal.

Memorandum submitted by the British Medical Association (10 March 1997) (CLE 6)

The interests of the BMA are focused not on the recent developments in cloning animals, but the ethical implications of the possible use of such technology in humans. Cloning human embryos by nuclear replacement is prohibited under section 3(3)(d) of the Human Fertilisation and Embryology Act (HFE Act). Cloning by embryo splitting is not prohibited by the Act but would require a licence from the Human Fertilisation and Embryology Authority (HFEA) which has announced that it will not issue licences for this procedure. The BMA currently supports this position. Cloning human embryos by embryo splitting without a licence from the HFEA would be an offence under the HFE Act.

Whilst recognising the possible benefits of embryo splitting for those undergoing fertility treatment, the BMA is concerned by the possible harm which could arise from cloning humans. If some of the cloned embryos were stored and implanted at a later date, for example, it is possible that identical children could be born years apart. The psychological effect of this on the children is unknown but could potentially be detrimental and for this reason the BMA supports a cautious approach. It is possible that cloning could be used to produce and store a cloned embryo in order to provide an identical sibling in case the existing child required a tissue transplant later in life, for example, or as a "perfect" replacement in the event of the child's death. Although it is possible that regulations could be put in place to prevent these occurrences, such as insisting that all cloned embryos are replaced in one treatment cycle, fundamental moral concerns remain about the cloning of humans. It has been suggested for example that cloning would undermine the intrinsic value of each person, dilute individuality and reduce the genetic variation on which species depend for their evolution and survival.

Having considered these issues in some detail, in 1994, the BMA supported the HFEA's decision not to issue clinics with licences for either research or treatment involving embryo splitting. The same and additional concerns arise where an existing adult, rather than an embryo, is cloned, as in the technique used in Edinburgh to create Dolly the sheep. The BMA is currently opposed to any cloning techniques being used in humans whether for research or treatment. As with all of the BMA's ethical guidance, this position will be kept under review but it is unlikely to change in the foreseeable future.

Memorandum submitted by Office of Science and Technology (10 March 1997) (CLE 7)

SHEEP CLONING

Introduction

1. The recently announced breakthrough in cloning from adult sheep cells at the Roslin Institute near Edinburgh is a further demonstration of the UK's pre-eminent position in biotechnology and the biological sciences. Developments in the animal and human health fields offer great promise for improved quality of life and present significant opportunities for technology transfer. However, this and similar developments raise a number of difficult and important questions about the ethics of experimentation, both in relation to animals and humans.

2. The Office of Science and Technology (OST) has an important transdepartmental role in helping to coordinate development of policy in biotechnology and bioethics, and to help strike a balance between the benefits and concerns raised by the science. It is also responsible for coordinating the Government's campaign to promote public understanding of science, engineering and technology (SET). The Minister for Science and Technology has responded to matters arising from recent public interest in cloning.

Science Base

3. It is widely accepted that the pace of scientific advance and the opportunities arising from this are at their greatest in the biological sciences and biotechnology. Genetic and biomolecular engineering and bioinformatics have emerged as two key priorities from the Foresight Programme.

4. In 1993 the Government decided to set up a discrete Biotechnology and Biological Sciences Research Council, recognising the strength of these disciplines in the UK's universities and research institutes and the capacity of active research users in the pharmaceutical, agriculture and other sectors to benefit accordingly. The Medical Research Council is also a major supporter of biotechnology research in the Higher Education and research institutes sector, particularly in relation to the applications of the technology in the medical field.

5. The evidence has grown ever clearer since 1993 that our research in this area is of the highest international quality, able to compete with the best anywhere in the world. In 1995 the Director-General of Research Councils published the results of a wide-ranging review of the science and engineering base which identified the UK as having world-class strengths in many of the biological sciences, especially at the molecular level. The review cited biosensors, photosynthesis, genetics, developmental biology, structural molecular biology and immunology.

6. Recent bibliometric analysis by the Office of Science and Technology indicates that the UK is in the top six in the world in plant and animal sciences (top ranking), agriculture, pharmacology, neuroscience, biology and biochemistry, microbiology, molecular biology and genetics, and psychology/psychiatry. This impressive concentration of excellence in the biological sciences is confirmed by the latest Research Assessment Exercise in which over 70 per cent of biochemistry units of assessment received a 5 or 5+ rating, compared with an average across all subjects of 20 per cent.

7. Bibliometrics have also demonstrated, repeatedly, that Research Council institutes in the field are up with the very best, world-class university departments both here and in the USA. In many respects the institutes share the qualities of university departments, engaging not just in research but the training of postgraduate students as well. The recent Prior Options reviews have confirmed the important role the institutes have to play in delivering longer-term, interdisciplinary basic and strategic research in the UK, and their reputation for excellent science.

Research at Roslin

8. These general characteristics of UK biological science and biotechnology are reflected in the Roslin Institute. It, too, took on a discrete existence as a self-standing BBSRC institute only in 1993, in recognition, among other things, of its close links with university and other research in the area, and the successful integration of molecular biology into its core programme.

9. Today its concentration on genome mapping, bioinformatics, and the application of molecular techniques to reproduction and development biology puts it centre stage. It is highly successful in winning competitive research grants. It has not only formed links with industry to develop its research, but spun-off some of its discoveries and activities in new companies. The Prior Options review concluded that Roslin should remain a BBSRC-sponsored institute.

10. Against this background, scientific breakthroughs of the kind achieved at Roslin first with Megan and Morag last year and now with Dolly should, perhaps, come as no surprise, though it is important to acknowledge the long-term nature of the enterprise—some ten years work—and the complexity of sustaining research over this time-span.

11. The most recent break-through came as one result of a £3 million research programme by MAFF (mainly at Roslin) in a project that also involved funding from the BBSRC, the EU and industry. BBSRC

core funding of Roslin will continue. MAFF funding for the specific project is winding down, but MAFF is planning to use some of the funds released from the sheep clonning research on related work at Roslin, for example on large offspring syndrome and to see if the technique can be made to work for cattle. The pharmaceutical sector has already been involved in supporting the research, and is pursuing its further development. It is open to the animal breeding industry to consider whether and how it might wish to take up the opportunities presented by the research.

12. Hand in hand with the scientific achievement and its potential applications come equally significant issues of appropriate regulation and public confidence.

A Coherent Approach

13. There is no doubt that the increasing frequency of breakthroughs in genetics research is posing a number of social and ethical questions. It is essential that our advisory and regulatory systems keep pace with developments in research. The system needs to be flexible enough to respond to new developments without presenting undue burdens to innovation and potential advances in human health and agriculture. It needs to reassure the public without damaging the quality of the scientific research output.

14. The Government has in place a variety of mechanisms to address the issues raised by advances in genetics; for example, the Ministry of Agriculture, Fisheries and Food established an ad hoc committe under the chairmanship of the Reverend Professor Michael Banner to consider the ethical implications of emerging technologies in the breeding of farm animals. The Ministry's policy on cloning of animals is guided by the recommendations of the committee.

15. However, the public debate since the announcement of the Roslin breakthrough has focused on human genetics. Groups in this field include a number of important bodies sponsored by the Department of Health which address specific human health issues, including the Advisory Committee on Genetic Testing, the Gene Therapy Advisory Committee and the Human Fertilisation and Embryology Authority.

16. In addition, the Government announced in July 1996 its intention to establish the Human Genetics Advisory Commission (HGAC), as recommended by the Science and Technology Select Committee. This group of eminent independent members takes an overview of developments in human genetics in their wider sense and is tasked to review scientific progress at the frontiers of human genetics; to report on issues that can be expected to have broad social, ethical and/or economic consequences; and to advise on ways to build public confidence in, and understanding of new genetics. The HGAC will consult widely and reports will be published.

17. The membership of the HGAC was announced in December 1996, and the group held its first meeting on 27 February 1997 to consider its work plan and outline its initial priorities. Members discussed the recent reports about new research on the cloning of sheep at the Roslin Institute. They noted that a method of cloning of human embryos by nuclear transfer is already expressly forbidden by the Human Fertilisation and Embryology Act 1990. They also noted that other forms of cloning to produce a human embryo, eg. involving nuclear replacement in an egg (the method used in the sheep) or embryo splitting, require a licence from the Human Fertilisation and Embryology Authority. The HFEA has decided not to licence the use of cloning either for treatment purposes, or for research directed towards treatment purposes, because it considers that this represents an unacceptable level of genetic manipulation and is neither necessary or desirable for treatment purposes.

18. It was agreed that the Chairman, Sir Colin Campbell, should write to the Chairman of the HFEA seeking to confirm the adequacy of the existing law. Sir Colin wrote on 3 March.

International Dimension

19. Scientific breakthroughs of this magnitude in the UK may have far-reaching implications for other countries too. The UK supports the view that all countries have the right to adequate controls over, in particular, human cloning. The UK has taken careful note of the inquiries launched by the Presidents of the European Commission and of the United States into the adequacy of Community and US national measures.

20. OST and the UK more generally will seek to play a full part in any international discussions which may emerge in this area. The Minister for Science and Technology discussed in December 1996 the regulation of genetics with the Carnegie Group of Science Ministers from G7 countries and Russia. To help provide a foundation for international debate, Mr Ian Taylor has written to the European Research Commissioner describing the main UK advisory and regulatory bodies in genetics research and this will be copied to members of the Carnegie Group. A copy of his letter is attached (Annex A).

ROLE OF OST

21. The secretariat to the Human Genetics Advisory Commission, which is sponsored jointly by OST and the Department of Health, is located within the Office.

22. OST chairs and provides the secretariat for the official Interdepartmental Group on Genetic Modification Technology (IGGMOT), which coordinates and develops cross-departmental policy on genetic modification technology, and coordinates the presentation of that policy in the EC and in international fora. A review[1] of the boundaries between departments' SET activities, published last December, recommended that the departments with the major interest in biotechnology and bioethics should jointly review the adequacy of present coordination arrangements, if possible before the end of this year. The Government's official committee on science and technology, EDS(O), has accepted the recommendation.

PUBLIC UNDERSTANDING

23. As part of its role in promoting public understanding of science, OST funds the British Association for the Advancement of Science to coordinate the National Week of Science, Engineering and Technology (SET Week). The purpose of SET Week is to present scientific information in a clear and accessible form. This is particularly important in areas such as biotechnology where the underpinning science is extremely difficult. SET Week is targeted at people of all ages and seeks to provide an understanding of scientific facts and processes as well as an appreciation of what benefits are offered and what cannot yet be achieved. Biotechnology will be a special focus this year (17-21 March).

24. Last summer the President of the Board of Trade launched the cross-Government Crusade for Biotechnology aimed at enhancing the UK's lead in Europe in the industrial exploitation of biotechnology, and for the UK to outpace international competitors in terms of industrial investment and growth over the next decade. Focused on competitiveness, the Crusade nevertheless recognises the importance of public confidence. Among 10 priority action areas for achieving this aim, identified in consultation with the science base and industry, is the need for *"Continued public confidence through public understanding of biotechnology and appropriate safeguards for human health and environment."*

Annex A

LETTER TO COMMISSIONER EDITH CRESSON, FROM MR IAN TAYLOR, MINISTER FOR SCIENCE (7 MARCH 1997)

The United Kingdom Government notes the initiative by President Santer, in the light of recent advances in cloning announced by the Roslin Institute in the United Kingdom, to initiate an examination of the implications of this research.

Genetic science generally has exciting potential to bring about benefits in areas such as health and agriculture, improving the quality of our lives. Cloning, for example, might, amongst other potential benefits, provide sources of production of important pharmaceutical products in animals' milk, and opportunities for treatment of mitochondrial disorders. To realise these benefits, however, it is vital that public confidence is maintained. The United Kingdom does not wish to see any over-burdening of new regulation in this area which might discourage research investment in the European Union, but it equally appreciates the need to prevent abuses of the new research.

We have over recent years developed a variety of mechanisms to address these issues in the United Kingdom. The emphasis has been on a flexible approach, capable of keeping pace with scientific developments, and providing a climate in which science can continue to flourish. Most recently, the Government has established a Human Genetics Advisory Commission whose role is to advise United Kingdom Health and Industry Ministers on the broad social, ethical and economic issues arising from developments in human genetics.

The Roslin Institute's pioneering research on sheep cloning has raised concern that this technology might be applied to human cloning. There is no question of this technique being applied to human beings in the United Kingdom. Cloning involving the creation of an embryo by replacing the nucleus of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo is expressly forbidden in the United Kingdom by the Human Fertilisation and Embryology Act 1990. Other means of cloning human embryos, such as embryo splitting would be allowed only under licence from the Human Fertilisation and Embryology Authority, which is a statutory body established under the Act. The HFEA has decided not to licence the use of cloning either for treatment purposes, or for research directed towards treatment purposes, because it considers that, at the present time, this represents an unacceptable level of genetic manipulation and is neither necessary nor desirable for treatment purposes.

[1] *Review of the Inter-Relationships Between the Science, Engineering and Technology Expenditure of Government Departments*, Office of Science & Technology, December 1996.

The United Kingdom believes that these arrangements provide a foundation for international debate. I am enclosing a memorandum which summarises our main advisory and regulatory arrangements in the genetics field. I hope that this will be helpful to the Commission and its advisers in tackling these important and challenging issues.

We would be happy to provide any further background which you require.

GENETIC RESEARCH

The Framework of Regulatory and Advisory Bodies in the United Kingdom

There are a number of advisory and regulatory bodies that the Government has established which have responsibility for examining the range of issues, including ethical issues, relating to genetic research. Some of these bodies advise on a statutory basis. A strong feature of the United Kingdom system is its flexibility. The main advisory and regulatory bodies are as follows:

A. Human Genetics

1. The *Human Genetics Advisory Commission* is a group of eminent independent individuals which was established by the Government in 1996 in response to a report by the House of Commons Science and Technology Select Committee. Its role is to take an overview of developments in human genetics and:

(i) to keep under review scientific progress at the frontiers of human genetics and related fields;

(ii) to report on issues arising from new developments in human genetics that can be expected to have wider social, ethical and/or economic consequences, for example, in relation to public health, insurance, patents and employment;

(iii) to advise on ways to build public confidence in, and understanding of the new genetics.

This group's first meeting was held on 27 February 1997 where it was agreed that it would carry out further work on issues such as genetics and insurance and genetics and privacy. The HGAC recognised that cloning of human embryos by nuclear transfer was already expressly forbidden by the Human Fertilisation and Embryology Act 1990. It was decided that the chairman of the Advisory Commission would write to his counterpart on the Human Fertilisation and Embryology Authority (HFEA-see below) seeking to confirm the adequacy of the existing law. A copy of the HGAC's press release is attached*.

The Advisory Commission is a non-statutory, non-regulatory body although it would be within its terms of reference to advise Ministers on the need for any legislation.

2. The *Human Fertilisation and Embryology Authority* (HFEA) was established in 1990 to oversee the implementation of the provisions of the Human Fertilisation and Embryology Act 1990. The Act expressly forbids the creation of an embryo by replacing the nucleus of a cell of an embryo with a nucleus taken from a cell of any person or embryo. The Act also states that a licence is required from the HFEA before any embryo can be created *in vitro*. The HFEA has decided not to issue licences for cloning either for treatment or for research purposes.

The HFEA is about to seek legal advice on the definition of some of the terms in the Act to clarify the implications for humans resulting from the recent cloning of sheep.

The HFEA is a statutory body and has a role in regulation of both research on embryos and of clinics which provide IVF treatment.

3. The *Advisory Committee on Genetic Testing* (ACGT) was established by the Government in 1996. It advises the United Kingdom Government on all aspects of genetic testing. Its terms of reference are:

(i) to provide advice to Ministers on developments in testing for genetic disorders;

(ii) to advise on testing individuals for genetic disorders, taking account of ethical, social and scientific aspects; and

(iii) to establish requirements, especially in respect of efficacy and product information, to be met by manufacturers and suppliers of genetic tests.

The ACGT is currently consulting on a voluntary code of practice for providers of genetic tests which are to be made available directly to the public.

4. The *Gene Therapy Advisory Committee* was established by the Government in 1993. This Committee brings together a wide range of medical, scientific, legal and lay expertise. Its terms of reference are:

(i) to consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;

* Not printed.

(ii) to work with other agencies which have responsibilities in this field including Local Research Ethics Committees and agencies with statutory responsibilities-the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment;

(iii) to provide advice to United Kingdom health ministers on developments in gene therapy research and their implications.

The Committee is a non-statutory, non-regulatory body. Its work is based on firm voluntary agreements with industry and academia.

5. Local Research Ethics Committees are non-statutory bodies which examine the ethical aspects of all proposals to carry out research on patients in the National Health Service. Their approval must be obtained before any such research can be conducted although this is done on a voluntary basis.

6. Other bodies which may examine genetic aspects of health care as part of a wider remit include:

The United Kingdom Xenotransplantation Interim Regulatory Authority which was recently established to provide advice on the use of animal tissue for transplant into humans and will advise on the need for regulation in this area;

The Medicines Control Agency which has statutory control of clinical trials of genetic medicines and licensing of such products.

B. Animal Genetics

1. The Animal Procedures Committee is an independent body set up under the United Kingdom Animal (Scientific Procedures) Act 1986 to advise the Government on matters concerned with the Act and the Government's functions under it. The Act regulates any experimental or other scientific procedure carred out on living vertebrate animals, or on Octopus vulgaris, which may have the effect of causing pain, suffering, distress or lasting harm. The controls extend to the production of genetically modified, protected animals. The Home Office has issued guidance on the operation of the Animal (Scientific Procedures) Act 1986 and the Biological and Biotechnological Sciences Research Council (BBSRC) has also issued guidelines on the use of animals in research. All applicants for BBSRC research grants are required to sign a declaration stating that they have read the Home Office guidance on the operation of the Act, including the Act itself, and that they agree to meet the conditions set out in the Council's own guidelines. The Act puts into effect European Directive 86/609/EEC.

2. The Ministry of Agriculture, Fisheries and Food (MAFF) established, under the Chairmanship of the Reverend Professor Michael Banner, an ad hoc Committee to "consider the ethical implications of emerging technologies in the breeding of farm animals". The Committee's report and the Government's response were published simultaneously on 28 February 1995. The Government accepted or agreed to consider further almost all of the Committee's recommendations and the Ministry's policy on cloning of animals is guided by the recommendations of the Committee.

C. Public Confidence in Biotechnology—Government Activities

The United Kingdom Government undertakes a number of activities aimed at improving public understanding of science. There are a number of initiatives which deal with developments in biotechnology. These include:

(i) A National Conference on Biotechnology is taking place on 10 March. This will examine inter alia the key issues regarding current controls and ethical concerns. The conference is being held in response to a recommendation in a report by the Government's Panel on Sustainable Development.

(ii) The "Crusade for Biotechnology" launched last year by the President of the Board of Trade with the overall aim of improving the competitiveness of United Kingdom biotechnology. Targets include continuing and increasing public confidence in biotechnology through public understanding of biotechnology and appropriate safeguards for human health, safety and the environment.

(iii) The Human Genetics Advisory Commission which aims to provide a focus for public concerns regarding human genetics.

(iv) The National Science Engineering and Technology week, which this year is taking place between 17 and 23 March and will have a special focus on biotechnology.

D. Other Relevant Bodies/Initiatives

1. The Advisory Committee on Genetic Modification advises the Government, its Health and Safety Commission and Health and Safety Executive on all environmental and safety aspects of the genetic modification of organisms in a contained environment. Much of its activity is carried out under Directive 90/219/EEC.

2. The Advisory Committee on Release to the Environment is a statutory body established to advise the Government on the deliberate release of genetically modified organisms. Much of its activity is carried out under Directive 90/220/EEC.

3. The Advisory Committee on Novel Foods and Processes (ACNFP) advises the Government on a number of food related issues including those related to genetically modified foods. Its remit is:

(i) To advise the Government on any matters relating to the irradiation of food or to the manufacture of novel foods or foods produced by novel processes, having regard, where appropriate, to the views of relevant expert bodies.

(ii) The ACNFP will continue to have this role after the EU Novel Foods Regulation has been implemented.

Memorandum submitted by the Ministry of Agriculture, Fisheries and Food (5 March 1997) (CLE 8)

Q1. *What research into cloning and related techniques was funded by MAFF at Roslin?*

MAFF has funded 10 projects at Roslin on cloning and related technologies. A list of the relevant project titles and funding is attached at Annex 1. Projects MS1201, MS1202, MS1209, MS1210 and LS1202 comprised MAFF's contribution to the production of cloned sheep.

Q2. *What were the reasons for funding this research?*

MAFF funded this work because of its long-term potential to contribute to more rapid genetic improvement of livestock than is possible with current technology. Healthy and productive livestock form the basis of efficient and safe food production and will benefit animals, farmers, consumers and the environment:

— the animals may benefit from improved ability to resist disease and parasites, or lower susceptibility to lameness or mastitis. It may also benefit animal species facing extinction;

— the farmer may benefit from improved animal fertility or improved feed conversion by animals;

— the consumer may benefit because farmers and the food industry would be better able to meet their demands;

— the environment may benefit, for example better feed conversion could result in less nitrogen being excreted.

Q3. *What consideration has MAFF given to ethical issues arising from the research?*

The Ministry's policy on the cloning of farm animals is guided by the recommendations of the Report of the Committee to Consider the Ethical Implication of Emerging Technologies in the Breeding of Farm Animals (the Banner Committee) which reported in 1995. They concluded that cloning may offer benefits and their major concern was "there have been problems with embryos produced by nuclear transplant or splitting causing overlarge calves and subsequent calving difficulties". Research is in place to address this question. Licences for the experiments leading to the scientific breakthrough were issued by the Home Office, as is the case with all experiments involving animals.

Q4. *What consideration has MAFF given to any intellectual property rights arising from the research?*

The research at Roslin leading to the production of the cloned sheep was funded by MAFF, BBSRC, the European Union and industry. MAFF generally retains 40 per cent of the intellectual property royalties from commissioned research (long-term strategic research) and 60 per cent of the intellectual property royalties from contracted research (shorter-term more focused research). MAFF-funded research at Roslin comprised both commissioned and contracted research, so the return on the research received by government will depend upon the proportion of the total funding provided by MAFF and the exact mix of commissioned and contracted research.

Q5. *Whether this funding is to be reduced and, if it is to be reduced, by how much and over what timescale, it is to be reduced?*

Funding for research on cloning *per se* is to be reduced. The research on sheep covered a number of approaches and has now been completed; industry is interested in taking it forward. Funds released from studies on sheep are being diverted to extending the science to cattle and research into problems with large offspring—a need identified in the "Banner" report.

Past and tentative future payments for Roslin for cloning and related work are as follows:

financial year	*1991–92*	*1992–93*	*1993–94*	*1994–95*	*1995–96*	*1996–97*	*1997–98*	*1998–99*	*1999–2000*	*2000–01*
payment £k	214	224	230	359	537	471	367	201	209	88

Q6. *(What are) the reasons for any such reduction (in funding)?*

The technique for cloning sheep is established and the funding has achieved its aims. MAFF funds strategic research until the science has been sufficiently developed for the work to be taken forward by industry or for the knowledge gained to be applied in policy formulation. The research on cloning of sheep is now ready to be taken forward by industry, in fact PPL (previously Pharmaceutical Products Limited) has already provided some of the funding and will take forward the medical application of this technology.

Memorandum from the Home Office (Constitutional and Community Policy Directorate) (CLE 9) (12.3.97)

Thank you for your letter of 11 March concerning the Report of the Committee to Consider the Ethical Implications of Emerging Technologies in the Breeding of Farm Animals (The Banner Report).

Recommendation (1)a of the Report (Harms of a certain degree and kind ought under no circumstances to be inflicted on an animal) is identified as a general principle which should be accepted as framework within which present and future uses of animals should be assessed. It implicitly recognises that the principle is not widely accepted, which is indeed the case.

The position under the Animals (Scientific Procedures) Act 1986 is that the Act does not identify any cost to animals as being in principle unacceptable. The Act requires that a cost benefit analysis is carried out whereby the costs to the animal(s) in a procedure are balanced against the benefits (for man, animals or the environment).

This is the method by which an application involving genetic modification would be assessed. It follows that whether a licence were granted or not would depend upon the application meeting these criteria. It is possible that harms considered elsewhere as intrinsically objectionable would be considered under the cost/benefit analysis. However, they would not automatically disqualify the application.

I attach with this letter* the most recent letter sent to Professor Banner concerning the establishment of adverse effects under the 1986 Act, and the extent to which it covered procedures that might be described as intrinsically objectionable. I think it is fairer to say that the matter is no longer under consideration by the Animal Procedures Committee, and that as yet Professor Banner has not replied to the attached letter.

It is correct to say that at present the Animal Procedures Committee does not routinely consider applications involving the genetic modification of mammals. It is hoped that measures will be introduced as soon to enable the committee to see some applications in this area, though not necessarily before a licence is granted.

Annex

LETTER TO PROFESSOR MICHAEL BANNER FROM RICK EVANS, HOME OFFICE (10.12.96)

Thank you for your letter of 4 September in which you ask whether the phrase "adverse effects" is to be construed sufficiently widely to include within its scope what might be deemed intrinsically objectionable modifications. I am sorry I have not replied before now.

Your report discusses the concept of intrinsically objectionable modification at some length and suggests that: "an intrinsic objection to a particular practice or action is an objection which does not relate to the practice's consequences or effects, but to the practice or action itself". Your letter goes on to provide an example of an intrinsically objectionable modification involving and resulting in a significant reduction of an animal's sentience: As I understand it, the intrinsically objectionable content of this example refers to the alteration of (something conceived of as) and essential nature, or the alteration of an evolved life form, which should be respected because it stands as part of the diversity of natural life. Within your framework, however, it appears that it is the original genetic modification which more properly represents the intrinsically objectionable practice rather than the *effect* of that modification.

The concept of an intrinsically objectionable modification seems to reflect a sense of affront stemming from religious or metaphysical beliefs. As such, it is not a concept which we find directly reflected in the Animals (Scientific Procedures) Act 1986 or in the world view on which the Act is based. In fact, an Inspector operating under the 1986 Act would consider the effects of an intrinsically objectionable modification, if there were any,

* *See* Annex below.

but he would not alter the definition of pain, suffering or distress he applied because the effects might be regarded elsewhere as stemming from an intrinsically objectionable modification.

As you know, there is a threshold definition of pain, now accepted across Europe, at and beyond which any scientific procedure is subject to the 1986 Act. This is set at the level of the pain which results from the insertion of a needle through the skin. The definition of suffering, distress and lasting harm is not subject to the same sort of criterion but judgements are made on a case-by-case basis, reflecting the experience and professional standing of the Inspector. This can involve reference to the judgements of expert peers in similar cases.

Any harm which (although imperceptible to an animal) might cause it pain, suffering and distress by rendering it vulnerable to elements in its environment would be considered as an adverse effect in terms of section 5(4) of the 1986 Act. Your example of an animal with reduced sentience would be considered here, if the animal were to be kept with other animals which had a higher level of sentience.

As for the general determination of adverse effects, it would be surprising of transgenic animals with any defect affecting the functioning of particular organs or tissues exhibited clinical signs dramatically different from those which would result from malfunction of the same organs or tissue from pathological causes. As such, they would be susceptible to diagnosis through the exercise of professional skills and judgement by veterinary surgeons. In my view, it would not be necessary or possible to define a range of clinical examinations or tests specific to transgenic animals.

Memorandum submitted by the IPMS (10 March 1997) (CLE 10)

The Committee will recall that, in October 1996, the Institution of Professionals, Managers and Specialists (IPMS) submitted detailed evidence to its inquiry into the Prior Options Reviews. Among the Institution's wide ranging scientific membership, detailed in that submission, are the scientific staff employed at the Roslin Institute, which have cloned the sheep "Dolly".

We recognise that the Committee is now engaged on a separate inquiry. It is not our intention to repeat our earlier evidence on Prior Options nor to comment on the legal or regulatory aspects of the nuclear transfer work at Roslin which, although important, are more properly within the remit of others. However on issues such as lack of continuity and uncertainty of scientific funding, which are commonly experienced across PSREs, there is a direct relevance to the specific difficulties currently being experienced at the Roslin Institute. (These are fully explained in the submission, dated 6 March, from the IPMS Section at Roslin). They must therefore be considered as part of the Committee's deliberations on the future of nuclear transfer work there.

The President of the Board of Trade announced as recently as 29 January that the Roslin Institute would be among PSREs retained in the public sector, and said that his decision "was designed to ensure that establishments operate with maximum effectiveness and efficiency, and to enhance the scientific excellence for which they are renowned". In other words, despite repeated efforts, the Government was unable to make a case for privatisation. This is an important admission, which echoes the views of the Levene team itself. Indeed, a member of the Levene team said in a meeting with the Council of Civil Service Unions that there was no justification for changing the status of Research Council Institutes because there had been no criticism of their management and they had emerged well from previous management reviews. The only sensible conclusion therefore is that RCIs, including Roslin, should be allowed a period of organisational and financial stability in which to pursue their work. As IPMS has repeatedly stated, long term research work will only flourish in an environment that provides security of funding and freedom from constant contractural and organisational upheaval.

Unfortunately, the Prior Options gave no guarantee of future funding. On the contrary, the Government and officials conducting the Prior Options Review never made any secret of their objective to squeeze more from the research budget at the existing or reduced level. In line with this, the Prior Options announcements came in fact in the same month as a Science Budget allocation which will ensure continued pressure on the funding of all except designated priority programmes. Yet, without an appropriate level of financial support, Ministerial statements in support of public science are both hollow and short sighted. IPMS has previously highlighted the danger of diverting funds from other research programmes and the wider science base. For example, MAFF imposed a 20 per cent overall reduction in funding for non-BSE research in BBSRC institutes, thus adversely affecting other important research projects including those at the Roslin Institute.

Leading edge research, such as that on nuclear transfer, cannot be satisfactorily developed in an environment in which funding sponsors are able without scientific justification to cut their level of support by half and repeatedly postpone funding decisions. As the Director of the neighbouring Moredun Research Institute has recently argued "We must beware (of) a mechanistic formula of science by numbers that leaves scant opportunity for curiosity, lateral thinking, inspired insights or sheer serendipity". In his view, and ours, Roslin "illustrates the attrition in long term stategic research by a policy of stop-go funding".

It has been stated MAFF's decisions regarding nuclear transfer research at Roslin complies with its contractural requirements. Leaving aside the problems in the operation of research by contract, addressed in previous IPMS evidence, it is fundamentally dishonest to argue on this basis that this work is not being cut. The IPMS Roslin Section state in their evidence that there are still many years of basic and strategic research required to improve the efficiency of nuclear transfer. This is surely a prime example of an issue on which the

Government's responsibility to safeguard the country's knowledge base requires the maintenance and development of a level of scientific expertise within its own domain sufficient to ensure continuing programmes of stategic and basic research and to meet demands for policy advice, standard setting and regulation.

It is also of the greatest importance that the intellectual property rights on the cloning technology continue to be held within the public sector. This is a vital, and highly sensitive, area of research and its development should not be subject to commercial interests. The fact that the Roslin Institute has worked in partnership with PPL Therapeutics is no reason to hand over to the private sector a key area of its research work. Moreover, the IPMS Roslin Section note that if PPL is the only source of funding, then the full potential of this technology will not be realised in the UK. Their warning that, in such circumstances, the UK's lead will be lost and the research transferred overseas is all too familiar. The Government must now act to prevent this loss of expertise.

The funding problems at the Roslin Institute are not unique, but are symptomatic of the damage done by successive rounds of cuts in public funding. Less than a year ago the Government's Chief Scientific Adviser conceded that spending cuts in MAFF had damaged the department's scientific capability at a time when public concern over issues such as BSE was growing. He stressed his view that "it is the reponsibility of all departments to take a broader view of their responsibility to respond to the unexpected" by maintaining their scientific expertise and that "We need to be thinking about how we respond to things we don't know about". There can be no more appropriate case than the nuclear transfer work being undertaken at the Roslin Institute.

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